GENE THERAPY: STATUS, PROSPECTS FOR THE FUTURE, AND GOVERNMENT POLICY IMPLICATIONS

HEARING

BEFORE THE

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

SEPTEMBER 28, 1994

[No. 168]

Printed for the use of the
Committee on Science, Space, and Technology

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*Ranking Republican Member.

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GENE THERAPY: STATUS, PROSPECTS FOR THE FUTURE, AND GOVERNMENT POLICY IMPLICATIONS

WEDNESDAY, SEPTEMBER 28, 1994

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The committee met, pursuant to call, at 1:49 p.m. in Room 2318, Rayburn House Office Building, Hon. George E. Brown, Jr. [chairman of the committee] presiding.

The CHAIRMAN. The committee will come to order.

We are in the midst of a roll call now, but we expect other Members to show up shortly, and I would like to get started in recognition of the fact that we have already been delayed a few minutes. I will begin with my opening statement.

Four years ago this month, a scientific event occurred that was so momentous and far reaching that some might have considered this science fiction come true. Scientists were, for the first time, able to actually repair defective human genes and replace them in the body of four-year-old Ashanthi DeSilva. This event was at once miraculous and threatening. No longer were humans born with defective genes doomed to a lifetime of suffering. Still, our understanding of the miracle and its implications is in its infancy.

Today, a healthy Ashanthi will appear before this committee as living proof that a miracle has occurred. While there are unanswered questions about the limits of this procedure, its promise is overwhelming. Therefore, the timing seems right to probe the state of the art.

The Science, Space, and Technology Committee has a long record of involvement in biotechnology and gene therapy issues, which dates back to the 1970s. Ray Thornton, Olin Teague, and I were all actively involved. We held numerous hearings and promoted some of the earliest legislation in the area. Subcommittee Chairman Thornton developed sufficient expertise that he was recruited for the Recombitant DNA Advisory Board where he served with distinction.

Later, then Representative Al Gore, as Chairman of the Investigations And Oversight Subcommittee, became very active in these issues. Perhaps most pertinent to today's topic was a series of three hearings Chairman Gore held in 1982, which contributed to the development of an innovative RAC review process.

During this hearing, we will look at the extent and nature of gene therapy research being constructed by the government, by

universities and by biotechnology companies; the ramifications of this research for human health, and the government policy options that will affect the ability to bring this technology to patients.

In our first panel, we will hear from representatives of the administration. Testimony will be given by Dr. Nelson Wivel, Director of the Office of Recombitant DNA Activities at NIH, who will be accompanied by Dr. Philip Noguchi, Director of Cellular and Gene Therapies of the Food and Drug Administration.

Actually, we will hear second from them and we will hear first from Dr. M.R.C. Greenwood, Associate Director for Science of the Office of Science and Technology Policy in the Executive Office of the President. These witnesses will give us an update on the research and development that is occurring throughout the Federal system as well as the importance of gene therapy for the competitiveness of the U.S. biotechnology industry.

Furthermore, we will hear of a recent change regarding NIH and FDA consolidated review of human gene transfer protocols.

In our second panel we will be privileged to meet with Ashanthi DeSilva and her father, Raj. Accompanying the DeSilvas is Dr. Kenneth Culver, one of the physicians that made up the NIH team that treated her with the gene therapy.

Our last panel consists of Dr. Jeffrey Swarz, Vice President of CS First Boston Corporation, an investment bank in New York, and Mr. Robert Abbott, President and CEO of Viagene, Inc. These witnesses will address the public policy issues which affect gene therapy research and the ability of gene therapy companies to raise capital.

Also to address this final panel will be Dr. LeRoy Walters, Professor of Philosophy at Georgetown University; and the Joseph P. Kennedy, Senior, Professor of Christian Ethics at Georgetown's Kennedy Institute of Ethics. Dr. Walters currently chairs the NIH Recombinant DNA Advisory Committee.

Dr. Walters will address the ethical issues involved with testing gene therapy clinical trials in humans and the Federal Government's role in ensuring that these ethical concerns are confronted appropriately and that we remain proactive in preventing serious ethical violations from occurring.

I might just as an aside mention that it would have been unheard of in the early days of gene therapy to have a philosopher and professor of Christian ethics serving on any of the appropriate committees, including chairing the DNA advisory committee, the RAC committee. So we have come a long way in that regard.

[The prepared statement of Mr. Brown follows:]

**Committee on Science, Space,
and Technology
U.S. House of Representatives**

**Opening Statement
George E. Brown, Chairman**

**Gene Therapy - Status, Prospects for the
Future, and Government Policy Implications**

September 28, 1994

Four years ago this month a scientific event occurred that was so momentous and far-reaching that some might have considered it science fiction come true. Scientists were, for a first time, able to actually repair defective human genes and replace them in the body of four-year-old Ashanti DeSilva. This event was at once miraculous and threatening. No longer were humans born with defective genes doomed to a lifetime of suffering. Still, our understanding of the miracle and its implications is in its infancy.

Today, a healthy Ashanti will appear before this Committee as living proof that a miracle has occurred. While there are unanswered questions about the limits of this procedure, its promise is overwhelming. Therefore, the timing seems right to probe the state of the art.

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Next we will hear from Dr. M.R.C. Greenwood, Associate Director for Science, of the Office of Science and Technology Policy in the Executive Office of the President. These witnesses will give us an update on the research and development that is occurring throughout the Federal system, as well as the importance for gene therapy for the competitiveness of the U.S. biotechnology industry.

Furthermore, we will hear of a recent change regarding NIH and FDA consolidated review of human gene transfer protocols.

In our second panel, we will be privileged to meet with Ashanti DeSilva and her father Raj. Accompanying the DeSilva's is Dr. Kenneth Culver, one of the physicians that made up the NIH team that treated her with the gene therapy.

Our last panel consists of Dr. Jeffery Swarz, Vice President of CS First Boston Corporation, an investment bank in New York; and Mr. Robert Abbott, President and CEO of Viagene, Inc. These witnesses will address the public policy issues which affect gene therapy research, and the ability of gene therapy companies to raise capital.

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We look forward to their testimony.

The CHAIRMAN. We will—let me ask if, do we have a Republican? Mr. Lewis will return shortly and Mr. Walker may come, and as soon as they appear, we will recognize them for any appropriate opening statement they may have.

I would like to ask if Mr. Valentine has any statement.

Mr. VALENTINE. Mr. Chairman, I thank the Chairman for recognizing me. I will be very brief, and say simply that I look forward to hearing from all of the witnesses, and in particular Ashanthi DeSilva and from her father Raj.

Ashanthi was benefitted—has benefitted, I am told, not only from gene therapy but also from a medication, PEG-ADA, which was developed by Dr. Michael Hershfield from the Duke University Medical Center. I, of course, take great pride that that institution is a part of my constituency.

And so I would simply like to say, in conclusion, I thank the Chairman for arranging the hearing. I think that as you have stated with great clarity, this is I think one of the most important sessions that we have had since I have been a Member of this committee.

I thank you, and yield back the balance of my time.

The CHAIRMAN. I certainly appreciate those comments. And I now turn to Mr. Walker if he is ready with any opening remarks that he might have.

Mr. WALKER. Thank you, Mr. Chairman.

Great strides are being made in the field of biomedical research, some of which we see even in today's media. Unfortunately, a lot of the things that are happening tend to be very costly and they have forced the private sector to seek increasing help from the Federal Government.

This raises two important questions. Will the government then be in a position of deciding which programs receive funding and thereby direct the research? And then, will that funding tail, so to speak, wag the overall scientific dog?

I look forward to today's testimony, and thank you for holding this important hearing as we begin to sort through those questions because they could very well determine the NIH of science and the NIH of Federal participation in science in the coming centuries. And I think what we are doing here is very, very important.

Thank you.

The CHAIRMAN. Mr. Lewis is the Ranking Republican on the subcommittee.

Do you have any opening statement, Mr. Lewis?

Mr. LEWIS. I ask unanimous consent to place it in the record.

The CHAIRMAN. Without objection.

Mr. Roemer, do you have anything?

Mr. ROEMER. Yes, Mr. Chairman, I would just make a very brief comment.

Sometimes events eclipse even the importance of a hearing today. I would associate myself with the remarks made by our distinguished Chairman and both Ranking Members with regard to the importance of this hearing.

But this is an important hearing for a variety of reasons, one of them being that we have a number of Members who have served so capably and ably on this committee for a number of years and

will not be coming back next term due to retirement. And a couple of them are here right now—Chairman Valentine, and Mr. Lewis, among the others, Chairperson Lloyd, Mr. McCurdy, Mr. Coppersmith, Mr. Bacchus and Mr. Grams.

And with respect to a couple of the people here, I would just like to say that I have very much enjoyed serving under the able leadership of Mr. Lewis, who has been always fair to me as a Democrat and has worked in a number of areas in a bipartisan way to cooperate on different endeavors, and certainly this body is going to miss him and this committee is going to miss him. And I am sure he will be inviting all of us down to Florida soon to enjoy the great beautiful weather down there.

Mr. Valentine, I have served under his very, very articulate and capable leadership, and I think it is especially important to note with him that so oftentimes around this body, you can meet people that you enjoy working with and that have a sense of humor and that you learn from, and then also that are very capable and knowledgeable about the legislative process. Not often do you have both those qualities in a Chairman.

And he is somebody that has served both as a mentor to me, giving me advice since my freshman year in 1991, and giving me and my wife, through his wife, Barbara, good ideas in different personal and legislative endeavors. So I would like to thank him and thank Chairman Lloyd, who is not here, but who hopefully will be coming here later. And especially people like Jim Bacchus who I served with and was elected with as a freshman.

But I would like to present to Mr. Valentine a small token of my appreciation and the committee's appreciation, a plaque for his service to the committee.

Mr. VALENTINE. Thank you very much.

Mr. ROEMER. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you for that very appropriate—

Mr. VALENTINE. Mr. Chairman, I know I am not entitled to it, but I just want to say publicly thank you very much. And—

The CHAIRMAN. Are you going to ask him when he is going to start taking some of that advice that he admired so much?

Mr. VALENTINE. No, Mr. Chairman. He takes it. He is a good student. I was simply going to ask that you maybe leave the record open in case any other Members who are not here would like to add their complimentary remarks.

The CHAIRMAN. As a technical matter, it is necessary for me to ask unanimous consent that today's hearings are opened to print and broadcast media, including still and video photography, and since there is no objection, that will be the order. And those pictures of you will be legal.

Bobby?

Mr. SCOTT. Just very briefly, Mr. Chairman, this subject is an example of how scientific advancement can cause—can raise many challenging questions, legal questions—business, profit-type questions, very many ethical questions. And I look forward, Mr. Chairman, to seeing how we can make scientific advancements and not get into some quagmires that obviously are developing in this particular subject. And I appreciate your calling this hearing.

The CHAIRMAN. Mr. Barca?

Mr. BARCA. Thank you, Mr. Chairman.

Just briefly, I also would like to echo the sentiments expressed by my colleague, Tim Roemer from Indiana. He expressed them far more eloquently than I could.

I want to thank Chairman Valentine. I had the pleasure of serving in his subcommittee, and we always had very interesting and important topics before us, as we do here today again.

And I wanted to say thank you very much publicly, Mr. Valentine, for your leadership and support. And my very best wishes to Mr. Lewis for his fine work on this committee and the others who will be retiring as well.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Mr. Barca.

And Mr. Hoke?

Mr. HOKE. Thank you, Mr. Chairman. And thank you for putting together this particular panel.

Much to my delight, I find that with us today will be two wonderful people who come from North Olmsted, Ohio, which I have the privilege of representing, including Ashanthi DeSilva, who is the daughter of Mr. Raj DeSilva, and Ashanthi was the first person in the United States to ever have been treated to cure the cause of a disease with gene therapy.

And so I am particularly happy to be here and to welcome them to Washington. And we will have the benefit of their testimony.

That's all I wanted to say. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Mr. Hoke.

I am glad that you called it to our attention. I was unaware that these witnesses were from your district or I would have allowed you special recognition for that purpose.

I would, in view of the comments that have been made about Mr. Valentine, indicate that I am going to honor him personally by asking him to take over chairing this hearing in about a half an hour, because of the fact that I have unfortunately some other commitments. And I want him to demonstrate in what has been his last full committee hearing the expertise which has earned him the accolades.

Mr. VALENTINE. Which you have heard about but never seen.

The CHAIRMAN. Which I have heard about but never seen.

Our first witness this morning will be Dr. M.R.C. Greenwood, better known as Marcie, Associate Director of the Office of Science Technology Policy at the White House, and we appreciate you being here, and welcome your testimony.

STATEMENTS OF DR. M.R.C. GREENWOOD, ASSOCIATE DIRECTOR FOR SCIENCE, OFFICE OF SCIENCE AND TECHNOLOGY POLICY, THE WHITE HOUSE; AND DR. NELSON WIVEL, DIRECTOR, OFFICE OF RECOMBINANT DNA ACTIVITIES, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DR. PHILIP D. NOGUCHI, DIRECTOR, CELLULAR AND GENE THERAPIES, FOOD AND DRUG ADMINISTRATION

Dr. GREENWOOD. Thank you, Mr. Chairman and Members of the committee. I am delighted to be here this afternoon to participate in the hearing on gene therapy status, prospects for the future and government policy implications.

What I'd like to do is talk briefly about gene therapy in the context of modern biology and then talk more specifically about a few issues that have been raised, and also about some plans to expand the opportunities for public participation in decision-making related to bioethics and gene therapy would be one of those issues.

We can certainly all appreciate that specific technologies have transformed our societies. For example, the Industrial Revolution turned this country from an agrarian-based society into one that is more dependent and rooted in industry and has in fact directed our future.

Many scientists and contemporary observers today believe that we are in the midst of a biological revolution, a tremendous biological revolution, and many of the ideas that are emerging from the field of biology are transforming our society. They are influencing how we view our relationship with nature, how we evaluate the quality of life, how we understand, diagnose and treat disease, and even how we define life and death.

The subject of today's hearing, gene therapy, then is both a derivative of our past and present scientific prowess, but it is also an indicator of a whole new set of future issues, scientific and ethical.

For decades we have known that height, hair and eye color are all traits that people inherit from their forebearers. We also know that some dreadful diseases come about as a consequence of having inherited a gene from one or both of our parents.

Some of the worst of these diseases devastate the lives of young children and their families and cost hundreds of thousands of dollars sometimes to treat. For the families of those afflicted, any approach that would prevent or cure such conditions would be worth the cost and many would welcome the information that would predict the disease as well.

But in addition to that, we know that a huge proportion of our population carries not a certain commitment to disease as some of these single-gene mutations do, but a predisposition to chronic disabling conditions that affect many of us and often take a lifetime to develop.

So when you put these together, that is, the inborn errors of metabolism, the single-gene diseases, the inherited-gene diseases and the predisposition that most of us carry toward chronic disease, the impact of our genes and the ability to regulate them or change their functions is relevant to virtually everyone in this country.

But before I go on and talk about gene therapy specifically, I want to point out that fixing genes and improving the health and quality of our life is completely consistent with our long-term goals of providing preventive and corrective medicine targeted to known individual needs of our citizens.

In the past, we had to focus, particularly in these inborn errors of metabolism, on relieving the symptoms of genetically determined disease. And for the future we believe that the opportunity to diagnosis, cure and alter the course of the disease is in front of us and very visible.

There is, to put it mildly, a significant degree of public interest in the nature and philosophy of gene therapy and its potential problems, but I want to cast it in a historical context. For example, in 1802 when Edward Jenner proposed injecting humans with ma-

terials from cows to vaccinate against smallpox, there was a great outcry illustrated by cartoons depicting people sprouting horns and tails.

So it is overwhelmingly important for the Congress to help the American people to understand the scientific discoveries that we're making and also to help the scientists understand the public's concern.

And so I commend you for having this hearing, because it is such an important part of the discourse that needs to go on in our public debate.

As a life scientist researcher, I spent about 25 years before I came to Washington trying to understand the genes that predispose all of us to diabetes and obesity. And if you look around the room, you will see this is of no small importance to many of us.

Today we know what chromosomes the genes that cause these diseases reside on. And you may have read in the media recently, in the past month or so, that the insulin-dependent diabetes gene—that's the one that occurs early, sometimes called juvenile diabetes, the form that afflicts young children—is regulated in part by genes that are known to be now on chromosomes 6 and 11. But there are as many as 18 other chromosomal regions that are also associated with the development of this disease.

So to be sure, from the scientific point of view these are not simple issues. In other words, some genetic diseases that can be traced to a single, simple problem in one individual gene may have some corrective prospects while numerous other familial diseases are linked to a highly complex set of coding faults. And we must understand as we're calling upon our biomedical investigators to solve these problems, that the problems they face are as complex as they are heartbreaking.

The most highly desired goal, of course, from the perspective of the patient and from the perspective of the country's health care system is to prevent the occurrence of disease. The bulk of our treatments today rely on ameliorating symptoms but they fall short of curing many patients. For those situations in which genetic elements are the causative agent, it does now stand to reason that the route to prevention and cure is through molecular biology and gene therapy.

While the promise is real, we do have to understand that we have a long ways to go before genetic medicine is a common, everyday practice.

The charter describing this hearing emphasized the goal of using gene therapy to direct inborn genetic defects that occur in humans. And that certainly is an appropriate goal. But I also want to point out that it is also going to be quite challenging.

The human genome, as you probably know, contains about 50 to 100,000 genes. The catalog, which we call the Mendelian Inheritance in Man, has about 4,200 known single-gene defects. About 300 or 400 have actually been cloned.

So the Human Genome Project is one of the current, ongoing scientific efforts that is playing a significant role in developing the research tools that have accelerated the pace of gene discovery. And

many human disorders are the result of interaction of several genes.

Gene therapy encompasses both the replacement of missing or defecting genes, such as you will hear from Ashanthi DeSilva and her father, but also augmenting the biological processes for fighting existing disease.

The first actual gene transfer protocol involved patients with cancer. The purpose of the trial was not therapy per se but to see if the genetically marked cells from a small group of patients would behave as predicted upon reintroduction into the patient's bloodstream. And I know that Dr. Wivel will describe these examples in more detail.

Another example of how complicated genetic intervention may be is that we may need to reach the genes in a specific organ like the islets of Langerhans, the part of the pancreas that is importantly disturbed in the cases of patients with diabetes.

It may not be feasible to rely on surgically removing target cells as a genetic practice in the future altering them and reintroducing them, we are going to have to create new ways of getting to the specific targets.

The early candidates for gene therapy are those defects that may be remedied in a simple fashion that introduces a gene that codes for a product that doesn't require careful regulation, but can be functional and useful in any amount while present in the general circulation and those have been some of the examples that have happened recently. But other candidates for gene therapy fall into the second category, treatments for diseases such as cancer and AIDS that work by boosting the patient's internal defense system.

And in addition, there are genes that require hormonal stimulation and have to be carefully modulated over time. Those will pose even more difficult choices and opportunities for investigation.

The point I want to underscore here is that a great deal of fundamental scientific research must be done in order to put the results of genetic studies to use in the diagnosis and treatment of disease. Continued support for the science will result ultimately in better quality, more cost-effective health care than we can provide today with our still rudimentary understanding of the genetic basis of disease.

Research in molecular biology and genetics is supported not only through the Human Genome Project, which I mentioned earlier, but also by virtually all NIH components, the National Science Foundation and many other agencies. And you will hear more about that from my colleagues here.

One concern that has been raised is that therapeutic regimens usually lag behind the technology used to diagnose illness. Prenatal genetic screening is now available for a number of conditions including Tay-Sachs, which is fatal to affected children between the ages of two and four.

To help inform the public discussion associated with identifying genes in the absence of appropriate gene therapies, we will have to continuously explain the scientific and ethical issues. That is one of the reasons in its position paper on research, "Science in the National Interest," we have pushed for programs to enhance public scientific literacy.

Enhancing our scientific literacy and our public understanding empowers our populace, it provides the means for informed decision making and providing a forum for airing tough issues, and exposing them to the scrutiny of experts and interested individuals is very important. This hearing makes an important contribution to increasing awareness of issues related to gene therapy.

The administration believes that the time has come for the Federal Government to assume a more proactive role in creating an atmosphere that fosters open discussion of thorny issues relating to biomedical and behavioral research and the applications of that research. That is why Dr. Gibbons and the Office of Science and Technology Policy has proposed establishing a national bioethics advisory committee.

The goal is to establish a panel of nongovernment experts in the relative scientific disciplines, law and ethics as well as community representatives, to provide advice and recommendations to the Federal Government. A draft charter for the national bioethics advisory committee was published on August 12 in the Federal Register and is up for comment now.

The commission would report to the President's National Science and Technology Council and would operate under the provision of the FACA. OSTP began developing this proposal at the request of the Departments of Energy and Health and Human Services in October of 1993.

These agencies had been considering establishment of a joint advisory panel to examine issues related primarily to maintaining the confidentiality of genetic information resulting from the Human Genome Project. However, it became quickly clear that there were a number of other bioethical issues that would benefit from consideration by such an advisory board.

Discussions took place with Members of Congress including Representative Markey, Senators Kennedy, Glenn, Hatfield and others. With their interest and encouragement, several important improvements were made in the early drafts. And the products of these drafts are the draft charter and the preamble which has recently been published in the Federal Register.

The immediate charge to the committee will be to consider issues in the protection of the rights and welfare of human research subjects and the management and use of genetic information. But the general charge will be to consider current and prospective issues pertinent to the conduct of research. And there will be an overarching principle to govern the ethical conduct of such research.

So, in summary, as we move forward in our search to prevent and cure human disease, it is critical that we support the fundamental science from which this new field is emerging and that we encourage the development of ethical guidelines for its application.

There is still a long way to go before the significant potential of gene therapy can be realized and put into general practice. As the research continues, we must also support efforts to communicate an awareness of its promise and limitations to get the public engaged in the dialogue.

Finally, we are going to have to look forward to training a new cadre of scientists, physicians and health professionals who are able to use this technology and its outgrowth for the future prevention of some of the diseases and the significant amelioration of others and whose practices— that is, this new cadre of physicians and scientists—are in the finest of ethical tradition.

Thank you, Mr. Chairman. That concludes my formal remarks.

[The prepared statement of Dr. Greenwood follows:]

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20500

Testimony of
Dr. M.R.C. Greenwood
Associate Director for Science
Office of Science and Technology Policy

before the

Committee on Science, Space, and Technology
U.S. House of Representatives

September 28, 1994

Good afternoon, Mr. Chairman, members of the committee. I would like to thank you for giving me the opportunity to participate in this hearing on Gene Therapy -- Status, Prospects for the Future, and Government Policy Implications.

Introduction

We can all appreciate that specific technologies have transformed societies. For example, the industrial revolution transformed this country from an agrarian-based society into one more dependent on and rooted in industry. Many scientists and contemporary observers of science believe that we are in the midst of a biological revolution. Many of the ideas emerging from the field of biology are transforming our society -- how we view our relationship with Nature; how we evaluate quality of life; how we understand, diagnose and treat disease; even how we define life and death. The subject of today's hearing, gene therapy, is both a derivative of our past and present scientific prowess and an indicator of a whole new set of future issues.

For decades we have known that height, hair and eye color are all traits that people inherit from their forebears. We also know that some dreadful diseases come about as a consequence of having inherited a gene from one or both parents. Some of the worst of these devastate the lives of young children and their families and cost hundreds of thousands of dollars, if not more, simply to relieve the pain and suffering in less than satisfactory ways. For the families of those afflicted, any approach that could prevent or cure such conditions would be worth any cost and many would welcome information that would predict whether they or a child would be affected by a genetic disease.

However, in addition to these traumatic and still rather rare inherited conditions affecting only a small group of patients, we now know that a huge proportion of the population carries not a certain commitment, but a predisposition to chronic disabling conditions which take a lifetime to develop such as diabetes and some forms of cancer and heart disease. When put

together, then, the impact of genes and our ability to modulate or change their function is relevant to virtually everybody in this country.

Before I go on and talk about gene therapy specifically, I want to point out that "fixing" genes and improving health and quality of life is completely consistent with our long term goals of providing preventative and corrective medicine targeted to the known individual needs of our citizens. In the past, we have had to focus only on relieving the symptoms of genetically determined disease. The future offers the opportunity to diagnose, cure and alter the course of disease.

There is a degree of public interest in the nature and philosophy of gene therapy, and its potential problems. This is not a new response to the advent of innovative therapeutic agents. For example, in 1802 when Edward Jenner proposed injecting humans with material from cows to vaccinate against smallpox, there was a great outcry illustrated by cartoons depicting people sprouting horns and tails. It is overwhelmingly important for Congress to help the American people to understand the scientists and also to help the scientists understand the public's concerns. We believe the Nation cannot afford to lose this opportunity to improve the lives of patients and cure these diseases. It also cannot afford to ignore the misunderstandings or mistakes that could develop and which thoughtful debate can prevent.

As a life sciences researcher, I spent 25 years before coming to Washington trying to understand the genes that predispose or cause diabetes and obesity; two diseases which, if you look around this room, are of great personal interest to at least some of us. Today, we know on which chromosomes the genes that cause these diseases reside in some animals, and have learned in the past month that insulin dependent diabetes mellitus, the form that so often and tragically afflicts young people, is regulated in part by genes on chromosomes 6 and 11, but that as many as 18 other chromosome regions may also be associated. So, to be sure, these issues are not simple. In other words, some genetic diseases can be traced to a single simple problem in one individual gene, while numerous other familial conditions are linked to a highly complex set of coding faults. We have to understand that the situations our biomedical investigators face today are as complex as they are heartbreaking.

Although there has been a resurgence of antibiotic-resistant strains, e.g., tuberculosis, antibiotics are largely adequate to manage many previously fatal bacterial infections and great strides have been made in curbing certain viral diseases. Vaccines are our most powerful weapon against the common infectious diseases of childhood--measles, mumps, rubella, and now Haemophilus influenza, as well as others such as hepatitis B. I characterize vaccines in this way because they actually prevent the occurrence of infection which is the most cost-effective approach to illness.

However, the medical armamentarium is still limited with respect to the prevention or treatment of many common chronic or long-term disabling diseases including arthritis, diabetes, heart disease, cancer, and mental illness. The most highly desired goal, from the

perspective of the patient and the country's health care system, is to prevent the occurrence of disease. The bulk of our treatment strategies for such conditions rely on ameliorating symptoms but fall short of actually curing patients. For those situations in which genetic elements are the causative agents, it stands to reason that the route to prevention and cure is through molecular biology and gene therapy. I think the promise is real, but we have a long way to go before genetic medicine is a common practice.

Questions Raised by the Committee

The charter describing the objectives of this hearing emphasizes the goal of using gene therapy to correct inborn genetic defects that occur in humans. Although truly Herculean, this is a worthy goal. The entire human genome is comprised of between 50- and 100,000 genes. Mendelian Inheritance in Man, the catalogue of genes associated with human disease now cites roughly 4,200 known single gene defects, of which only 300 to 400 have actually been cloned. Many of these genetic defects are responsible for known rare metabolic diseases such as Tay-Sachs and Gaucher, or other pathological conditions including sickle cell anemia, cystic fibrosis and familial hypercholesterolemia. The Human Genome Project has played a significant role in developing the research tools that have accelerated the pace of gene discovery. As noted before, many more human disorders are the result of the interaction of several genes, thereby compounding the difficulties in getting to the root causes. When the role of genetic susceptibility to environmental influences is added to this already complex equation, the true magnitude of the long term task becomes apparent.

Current State of Gene Therapy

Gene therapy encompasses both the replacement of missing or defective genes and augmenting existing biological processes for fighting disease. Although it was expected that the first applications of gene therapy would be directed toward correction of genetic defects, in fact, that has not been the case. The first actual gene transfer protocol involved patients with cancer. The purpose of this trial was not therapy, per se, but to see if genetically "marked" cells from a small group of patients would behave as predicted upon reintroduction into the patients' bloodstream. I know that my colleague Dr. Wivel will describe these examples in more detail later. The point I want to emphasize is that we are at a very early stage in the development of this technology. The first targets for gene therapy trials will be determined by the available scientific capabilities. Some of the thousands of diseases caused by just the tiniest change in a patient's genetic code may not be treatable using these methods for quite some time. The reasons for such limitations are varied but I will describe just a few.

Almost all inherited metabolic disorders are the result of improperly functioning proteins, especially enzymes. Enzymes are the catalysts that permit us to extract nutrients from the food we eat, to transfer energy enabling us to perform tasks, to send signals from one cell to another, and to detoxify and excrete the endproducts of these life processes. Enzymes are essential to life and a defect in the gene coding for these compounds would be lethal to the

developing fetus. Every living organism relies on the appropriate enzymes being present at the right time and in the right amounts. Therefore, the simple replacement of a defective gene may not be sufficient to improve the condition of the patient. Exquisitely fine regulation of production of the enzyme at the molecular level is also crucial in some cases.

Another example of how complicated genetic intervention can be is the fact that we may need to reach the genes in a specific organ like the islets of Langerhans in the case of patients with diabetes. It may not be feasible or practical to rely on surgically removing the target cells, altering them in a petri dish in the laboratory and returning them to the patient. Other options include creating methods that will enable the replacement genetic material to home in on the target cells or tissues, such as using viral delivery systems that are already accustomed to reaching the desired cells, or selecting for treatment those conditions that can be remedied without need for such specificity. Both of these options are under study.

The early candidates for gene therapy therefore, are those defects that may be remedied in a fairly simple fashion by introducing a gene that codes for a product that does not require careful regulation but can be functional and useful in any amount while present in the general circulation. Other candidates fall in the second category that I mentioned, as treatments for diseases such as cancer and AIDS that work by boosting the patient's internal defense systems. For now, the selection of disease targets is limited by the available science and technology. As we learn more and more about regulation of gene expression in the normal organism, we will be able to apply this to our understanding of disease processes.

I think it is fair to say that today's biomedical investigator has , for the first time, the scientific knowledge and technological tools to begin addressing questions that have eluded us in the past. The answers open doors to additional avenues of investigation, bringing us closer to understanding the fundamental biological processes underlying normal and disease states. This knowledge, in turn, points toward means to diagnose, treat and, ultimately, cure or prevent disease.

Breast Cancer Susceptibility Gene

The recent identification of a breast cancer susceptibility gene is a good illustration of this process. Although the existence of a gene associated with inherited forms of breast and ovarian cancer was postulated in 1990, it was just two weeks ago that the precise chromosomal location of the gene was announced, prior to publication in SCIENCE, the journal of the American Association for the Advancement of Science. Mutations in this gene are thought to account for one-half of the 5 percent of cases of hereditary breast cancer, which often strikes women at a relatively early age. Breast cancer is diagnosed in approximately 180,000 American women each year and the race to find this gene was intense, involving several groups of researchers. The team that made this finding was headed by scientists from the University of Utah Medical Center and Myriad Genetics, Inc., in Salt Lake City; and the National Institute of Environmental Health Sciences, North Carolina-based component of the National Institutes of Health.

I think it is worth paraphrasing a statement made by one of the scientists that locating the BRCA-1 gene creates more questions than it answers. With this key gene in hand, we can begin to examine the entire cascade of events that lead up to the development of breast cancer, including, perhaps, the 95 percent of cases that are not hereditary. We also expect that this discovery may be extended to helping to understand the normal forces that regulate cell growth and cell division and how disruption of this function leads to cancer. Of course there is immediate interest in using the gene to develop a screening test to identify women at increased risk of inherited breast cancer and ovarian cancer. This will take some time -- time we will need to identify and establish procedures under which such tests would be helpful.

I will return to the issue of ethics and genetic information in a moment. The point I want to underscore is that a great deal of fundamental scientific research must be done in order to put the results of genetic studies to use in the diagnosis and treatment of disease. Continued support for the science that offers such tremendous promise will result ultimately in better quality, more cost-effective health care than we can provide today with our still rudimentary understanding of the genetic basis of disease. Research in molecular biology and genetics is supported not only through the Human Genome Project, but also by virtually all NIH components, the National Science Foundation and many other agencies. I believe you will hear more about this work from Dr. Wivel. We must not lose sight of the long-term value of this commitment.

The discovery of the breast cancer susceptibility gene and the attention it generated in the press offers a useful opportunity to educate the public about the power and limitations of biomedical science. Dr. Varmus and the NIH scientists deserve the credit for explaining what this discovery means for women at risk of breast cancer and for the public at large. When this announcement was made, we were gratified to see that the press showed great sensitivity in explaining that a screening test would not be forthcoming immediately. But questions about who should be screened and under what conditions have been raised and should be fully aired, even before such a test becomes available.

Issues to be Discussed

Similar questions have surfaced to accompany other medical achievements. One concern that has been raised is that therapeutic regimens usually lag behind the technology used to diagnose illness. For example, prenatal genetic screening now is available for a number of conditions, including Tay-Sachs, which is fatal to affected children between the ages of 2 to 4. Other diagnostic tests may be easier to consider if the condition, such as colon cancer, is treatable with early detection. Nonetheless, the vexing question of how to utilize information on genetic disease or predilection in the absence of a cure will remain of intense interest to our citizens.

To help inform the public discussion, we will have to continuously explain the scientific and ethical issues. That is one of the reasons that in its position paper on research, Science in

the National Interest, the Administration has pushed for more programs to enhance public scientific literacy. Enhancing our scientific literacy empowers our populace, providing the means for informed decisionmaking. Providing a forum for airing tough issues and exposing them to the scrutiny of experts and interested individuals is also important. This hearing makes an important contribution to increasing awareness of issues related to gene therapy. I think the early public interest in human gene therapy protocols, before the technology was in hand, also played a role in resolving some reservations and permitting approval of this work.

National Bioethics Advisory Commission

The Administration believes that the time has come for the Federal government to assume a more proactive role in creating an atmosphere that fosters open discussion of thorny issues related to biomedical and behavioral research and the applications of that research. That is why Dr. Gibbons and the Office of Science and Technology Policy have proposed establishing a National Bioethics Advisory Commission. The goal is to establish a panel of non-government experts in the relevant scientific disciplines, law, and ethics, as well as community representatives, to provide advice and recommendations to the Federal government. In order to engage broader public participation in the discussion of such a group's role and composition, a draft charter for a National Bioethics Advisory Commission was published on August 12 in the *Federal Register* for comment. The Commission would report to the President's National Science and Technology Council and would operate under the provisions of the Federal Advisory Committee Act.

OSTP began developing this proposal at the request of the Departments of Energy and Health and Human Services, in October 1993. These agencies had been considering establishment of a joint advisory panel to examine issues related to maintaining the confidentiality of genetic information resulting from the Human Genome Project. It became clear that there were a number of other bioethical issues that would benefit from consideration by an expert, standing advisory body. Thus, the informal interagency working group was expanded to include representatives of DOD, NASA, VA, NSF and Justice. Discussions also took place with members of Congress including Representative Markey and Senators Kennedy, Glenn and Hatfield. With their interest and encouragement, several improvements were made in early drafts. The products of these discussions are the draft charter and preamble which have been recently published in the *Federal Register.*

The key points of the charter are:

- The immediate charge to the Commission will be to consider issues in the protection of the rights and welfare of human research subjects and management and use of genetic information.

- The general charge to the Commission will be to consider current and prospective issues pertinent to the conduct of research on human biology and behavior and to identify broad, overarching principles to govern the ethical

conduct of such research. The Commission would have broad authority to establish its own priorities and agenda, in accordance with the following four criteria:.

1. Public health or policy urgency of the bioethical issue;

2. Relation of the issue to the goals for Federal investment in science and technology;

3. Absence of another body able to fruitfully deliberate on the issue; and

4. Extent of interest in the issue across the government.

The Commission would accept input on potential issues for consideration from the National Science and Technology Council, Congress and the public at large.

- The Commission would be composed of experts in the fields of bioethics and theology, social and behavioral science, law, medicine and biological research, in addition to representatives of the general public. Its members would be appointed by the President.

You may recall the groundbreaking work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research; reports such as Defining Death, Splicing Life and Research Involving Children. It is our hope that this new group would build upon the impressive body of collective wisdom generated by earlier commissions. We believe that the Commission would be useful in considering some of the difficult issues that will be discussed today.

Summary

As we move forward in our search to prevent and cure human disease, it is critical that we support the fundamental science from which this new field is emerging and that we encourage the development of ethical guidelines for its applications. There is still a long way to go before the significant potential of gene therapy can be realized and put into general practice. As the research continues, we must also support efforts to communicate an awareness of its promise and limitations and get the public engaged in the dialogue. Finally, we must look forward to training a new cadre of scientists, physicians and health professionals who are able to use this technology and its outgrowths in the future for the prevention of some diseases and the amelioration of others and whose practices are in the finest ethical traditions.

I thank you for your attention and offer to answer any questions you might have.

The CHAIRMAN. Thank you very much, Dr. Greenwood.

We will call on the other two panelists before questioning the panel as a whole.

Our next panelist is Dr. Wivel, who is—Dr. Nelson Wivel, who is Director of the Office of Recombinant DNA Activities at NIH. He has had a distinguished research career there for many years and holds a position of high responsibility in this field and we welcome his appearance here this morning.

Dr. WIVEL. Thank you, Mr. Chairman and Members of the committee.

I am pleased to be here today to participate in a review of the status of gene therapy research in the United States and to participate in a discussion relating to the future prospects for this particular type of biotechnology.

In 1974, the Office of Recombitant DNA Activities was established at National Institutes of Health in response to concerns raised by the scientific community regarding the safety of manipulating microbes and cells through the use of recombinant DNA techniques.

The Director of the NIH established the Recombinant DNA Advisory Committee, commonly known as the RAC, to advise him, the Assistant Secretary of Health, and the Secretary in the Department of Health and Human Services, on matters relating to research involving recombinant DNA.

There are 25 members who serve on the RAC, 16 are scientists and nine are public members who represent the fields of law, ethics and public policy.

The first task of the RAC was to develop a set of guidelines that were intended to prevent unintended release or exposure to genetically modified organisms. The NIH guidelines for research involving recombinant DNA molecules were first published in 1976. They have been revised frequently since then and the latest edition was released July 5 of this year.

In the first years of this committee's existence, the Members were fully occupied with setting national standards for laboratory research and human gene therapy was not even on the agenda.

In the early 1980s, a Presidential commission produced a document entitled "Splicing Life," and the RAC was asked if it wished to respond to this report. The RAC responded affirmatively and a subcommittee was formed to yield a mechanism for the conduct of gene therapy reviews.

Their efforts yielded a document called "The Points to Consider." And the directives included in this document have been incorporated into the NIH guidelines.

The first protocol for the study of a genetic deficiency disease, adenosine deaminase deficiency, was approved by the RAC on July 31st, 1990, and the first patient was treated on September 14th.

What has happened during the intervening four years?

While the initial supposition was that gene therapy would be used primarily for genetic deficiency diseases, 63 of the first 90 protocols approved by the RAC have involved the study of cancer. There are six protocols for the investigation of AIDS.

Of the single-gene deficiency diseases, the most intense research activity has involved cystic fibrosis, with 10 protocols approved.

Perhaps this shouldn't be surprising since cystic fibrosis is the most common genetic deficiency disease in this country.

Six other types of single-gene deficiency diseases are being studied and two recent research proposals involved patients with rheumatoid arthritis and peripheral artery disease, indicating the rather wide scope of application of gene transfer techniques.

What is the nature of the results thus far?

Despite the diversity of diseases that are targets for genetic intervention, essentially all the protocols seen to date share common features in that these are early trials and the principal information includes data about safety, tolerance for the procedures, and expected and unexpected toxicities.

Also, the therapeutic benefits possibly may be observed, therapeutic efficacy cannot be construed as the primary goal for these Phase I studies.

With regard to the cancer studies, the most significant finding to date is the result of using gene transfer techniques to answer an important question about the biology of leukemia. There was no therapeutic intent in performing gene transfer, but the results have had very important connotations for the treatment of leukemia.

Bone marrow transplantation is often indicated in the treatment of leukemia. When matched or compatible bone marrow transplants are unavailable patients have frequently been treated with their own bone marrow. Although this marrow is harvested in periods of clinical remission, there has always been concern that it might contain cancer cells.

When patients relapse following bone marrow transplantation, it has not been clear whether the current disease had its origins in the transplanted bone marrow or in remaining malignant cells in other parts of the body. As a result of gene transfer studies of bone marrow cells, it has been possible to detect these gene-marked cells when recurrent disease was detected. As a result of these findings, new methods of purging the bone marrow are being tested to help ensure that leukemic cells can be removed from the transplant.

Although the published literature is quite small, the studies of genetic deficiency disease indicated the following: normal genes can be inserted into cells; these gene-modified cells can be given to patients; and the genes will function to produce a normal gene product for limited periods of time, often for a few days and occasionally for longer periods of time.

Because of the limitations in the current technology, the number of cells actually treated is relatively small, and it would not be realistic to expect significant changes in the disease process.

A careful assessment of gene therapy must acknowledge that it is in its early stages. While the current research is highly experimental, there is every reason for optimism. It bodes well that gene transfer is being applied to genetic deficiency diseases and diseases of major incidence such as cancer, cardiovascular disease and AIDS.

If effective treatments can be developed, and if gene delivery systems can be refined, the expense of this type of intervention can be justified, particularly when the costs of the various categories of disease are considered in the context of disability, abnormal short-

ening of life-span and the use of treatments that are palliative at best.

As you might anticipate, the United States has the clear lead in this type of research. There have been a few gene-transfer experiments in the United Kingdom, France, the Netherlands, Italy, and one trial in the People's Republic of China that was conducted by an investigator trained in the U.S.

The United Kingdom has probably gone farther in establishing organized review procedures than most of the other countries. Their Genetic Therapy Advisory Committee, commonly known as GTAC, represents a close analog to the RAC.

At this juncture, I would like to switch topics slightly and make a few comments about the consolidated review process involving the NIH and the FDA. As a regulatory agency, the FDA is required to review all gene therapy protocols. The NIH's RAC reviews protocols in which the investigators or their institutions receive NIH funding for recombinant DNA research. If no NIH funding is involved, then the protocol doesn't have to be brought before the RAC.

NIH reviews are conducted in public, and FDA reviews have been conducted largely in private, given the requirement for FDA to protect proprietary information.

On July 18th and 19th of this year, the National Task Force on AIDS Drug Development held an open meeting for the purpose of identifying barriers to AIDS drug discovery. And this included a proposal to streamline the dual-review process for human gene therapy experiments. Members of the task force recommended a consolidated review process to allow the RAC to selectively review protocols.

As a result of the task force deliberations, recommendations were adopted in order to eliminate any unnecessary overlap between the NIH and the FDA in their review of human gene therapy protocols. Both doctors Varmus and Kessler noted that their respective agencies would cooperate fully to effect the changes necessary to implement these recommendations.

At its meeting on September 12 and 13 of this month, the RAC approved in concept the suggested changes in the review process. The specific recommendations are as follows: the NIH and FDA recommend that the RAC become advisory to both the NIH Director and the FDA with regard to the review of human gene transfer protocols.

In the interest of maximizing the resources of both agencies, and in simplifying the method and period of review of research protocols involving human gene transfer, it is planned that the FDA and NIH institute a new consolidated review process that incorporates the following principal points.

One, all gene transfer protocols shall be directly submitted to the FDA.

Two, upon receipt, FDA review will proceed. Staff members of the Office of Recombinant DNA Activities at NIH, members of the RAC, and FDA staff will decide on the necessity for full RAC review.

Three, factors which will define the need for RAC review include: use of new vector systems for gene delivery, targeting of new dis-

eases for study, unique applications of gene transfer, and ethical issues that require further public review.

Four, whenever possible, principal investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required.

Five, semiannual data reporting procedures will remain the responsibility of NIH. Semiannual data reports will be reviewed by the RAC in a public forum.

Six, the RAC and the FDA will broaden their scope of activities in gene transfer to jointly and prospectively address global issues beyond the matter of individual protocol review. The RAC charter allows for the creation of subcommittees or working groups to address issues of special interest, for example, ethics and the implementation of a gene therapy patient registry, access for orphan genetic disease patients for therapies and criteria for prenatal gene therapy.

Staff members of the NIH and FDA are continuing to work on the implementation of this proposal with the goal of having the plan operational by the end of calendar year 1994.

This completes my formal remarks.

[The prepared statement of Dr. Wivel follows:]

United States House of Representatives
Committee on Science, Space and Technology
Representative George Brown, Chairman

Hearing on Gene Therapy - Status, Prospects for the Future
and Government Policy Implications
September 29, 1994

Written Testimony of
Dr. Nelson A. Wivel
Director
Office of Recombinant DNA Activities (NIH)

Mr. Chairman, and members of the Committee, we are pleased to be here today to participate in a review of the status of gene therapy research in the United States, and to participate in a discussion relating to the future prospects for this particular type of biotechnology.

I am Dr. Nelson Wivel, Director of the Office of Recombinant DNA Activities at the National Institutes of Health, and I have the responsibility for administering the Recombinant DNA Advisory Committee. I am accompanied by Dr. Philip Noguchi who is Director of the Division of Cellular and Gene Therapies in the Center for Biological Evaluation and Research at the FDA.

CURRENT STATUS OF HUMAN GENE THERAPY

Events in the Development of Gene Therapy

The Office of Recombinant DNA Activities (ORDA) was established in 1974 in response to concerns in the scientific community regarding the safety of manipulating microbial and cellular genomes through the use of recombinant DNA techniques. The charter for the Recombinant DNA Advisory Committee (RAC) was approved on October 7, 1974. The RAC was formed by the Director of the NIH for the purpose of advising him/her, the Assistant Secretary for Health, and the Secretary of the Department of Health and Human Services on matters relating to research involving recombinant DNA.

Following the Asilomar Conference in California where scientists discussed their concerns about using recombinant DNA techniques as a research tool, the RAC began to develop a set of guidelines that were intended to prevent unintended release or exposure to genetically modified organisms. *The NIH Guidelines for Research Involving Recombinant DNA Molecules* were first published in 1976 and have been revised periodically since then, the latest edition being published on July 5, 1994. These guidelines apply to all investigators receiving NIH funds for research involving recombinant DNA. In contrast to regulations, the guidelines can be amended easily, and the changes are predominantly science-driven.

In the first years of its existence, the RAC was fully occupied with setting national standards

for the conduct of laboratory research, and human gene therapy was not even on the agenda. In 1980, two events occurred that provoked an interest in gene therapy. First, religious leaders representing all the major faiths sent a letter to President Carter expressing concerns about the problems inherent in genetic engineering. Second, it was discovered that Dr. Martin Cline had collaborated in unapproved attempts at gene therapy in order to treat two patients who had beta-thalassemia, a serious blood disorder. A President's Commission on Bioethics was formed and a congressional hearing was convened by then-Congressman Albert Gore, Jr in 1982 to consider the problems and opportunities associated with human genetic engineering. The Presidential Commission produced a document entitled *Splicing Life,* and in 1983 the RAC was asked if it wished to respond to this report. The RAC responded affirmatively and a subcommittee was formed for the expressed purpose of creating a mechanism for the conduct of human gene therapy reviews. A document was created, and it was called the "Points to Consider;" the directives included in this document have been incorporated into the *NIH Guidelines* as Appendix M. This public review process that was designed in 1984 and 1985 was first used in the review of a clinical protocol in 1988 when a gene-marking study was evaluated. This particular protocol was presented as a prologue to subsequent procedures, and the principal intent was to establish that the use of a particular kind of gene delivery system (retrovirus vector) was safe to use in research subjects. The first protocol for the treatment of a genetic deficiency disease (severe combined immune deficiency caused by adenosine deaminase deficiency) was approved by the RAC on July 31, 1990 and the first patient was treated on September 14, 1990.

Definition of Human Gene Therapy

For the purposes of this statement, human gene therapy can be defined as those techniques that allow a functioning gene to be inserted into the somatic cells of a patient to correct an inborn genetic error or to provide a new function to the cell. In the matter of genetic deficiency diseases, the use of gene therapy provides an important new concept for medical treatment in that it focuses on the genetic cause of the disease rather than being focused on ameliorating the consequences of the disease. In the matter of providing a new function to the cell, genes can be inserted into cells to make them perform tasks that normally would not be performed. For example, genes are deliberately introduced into cancer cells to make them susceptible to killing by the patient's own immune system.

All research that is currently being done is somatic cell gene therapy, and there is a specific prohibition of any proposals that would introduce genes into the reproductive cells (sperm or ova) of a patient (germ-line gene therapy). The scientific developments necessary to even contemplate germ-line gene modification are many years away and present additional problems to those faced in somatic cell gene modification.

Elements of RAC Review of Human Gene Therapy

In order to gain approval of a human gene therapy protocol, there are a number of submission requirements that must be met and these are detailed in the *NIH Guidelines* in

Appendix M, the *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects.* A series of questions must be answered for each protocol.

In the description of the proposal, the objectives and rationale of the proposed research must be stated. For research in which recombinant DNA is transferred in order to treat a disease or disorder, the following questions must be answered. Why is the disease selected for treatment by means of gene therapy a good candidate for such treatment? What objective and/or quantitative measures of disease activity are available? Are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene therapy? Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims? What alternative therapies exist, and what are their relative advantages and disadvantages as compared with the proposed gene therapy?

The investigator is requested to provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following kinds of questions must be answered. What is the structure of the DNA that will be used? What is the complete nucleotide sequence analysis or detailed restriction enzyme map of the gene and the delivery vehicle (vector) for the gene? What are the steps used to derive the DNA construct? What regulatory elements does the DNA construct contain?

Data from preclinical studies, including risk-assessment studies, must be provided. The results must demonstrate the safety, efficacy, and feasibility of the proposed procedures using animal and/or cell culture model systems. The cells that are the intended target cells of recombinant DNA must be identified, and the efficiency of the delivery system must be determined, including the percentage of the target cells that contain this added DNA. There must be data to address the stability of the recombinant DNA in terms both of its continued presence and its structural stability. It is also necessary to determine the minimal level of gene transfer and expression that is estimated to be necessary for the gene therapy protocol to be successful in humans.

Most of the gene delivery systems have involved the use of viruses and the following types of information have to be provided. The stability of the virus vector must be established. If such a vector is likely to undergo structural rearrangement or mutation, if it is likely to regenerate infectious particles, or it is likely to cause an immune reaction, it would not be a good candidate for use. In the case of non-viral delivery systems, such as lipid or fat molecules, it is necessary to perform animal studies to determine if there are pathological or other undesirable consequences of their use.

Investigators are required to provide comprehensive details about clinical procedures including the methods for monitoring the patients. The cells that will receive recombinant DNA must be identified, the method for administering the treated cells must be described,

the cell volume must be quantified, and the treatment schedule must be described. Clinical endpoints must be established, and there should be some quantitative measurements to assess the specific effects of this intervention on the natural history of the disease. The frequency of the follow-up studies must be indicated; in many cases it is desirable to follow the patients for life.

In addition to the specific information about the protocol itself, there are public health considerations that must be addressed. It has to be determined if there is a possibility that the recombinant DNA will spread from the patient to other persons or to the environment. Special precautions may be necessary to assure that family members or health care workers are not at risk. One of the possible side effects of somatic cell gene therapy is the unintended transfer of the gene to reproductive cells. In patients who are of child-bearing age, birth control measures may be necessary and the selection of patients for a given study will have to reflect this necessity.

Selection of patients is another critical element that has to be addressed, and it is important to establish inclusion and exclusion criteria, both for the sake of the patients and in the interest of deriving the most possible information from the study. In some cases it may be necessary to establish special procedures when it is not possible to include all patients who desire to participate in a study.

In addition to scientific and clinical considerations, one of the most important elements in this type of research is the informed consent document. Because of the relative novelty of the procedures that are used, the fact some consequences of the procedures may not be reversible, and the reality that some of the potential risks may be undefined, it is incumbent that the investigators disclose the critical elements of the study to patients, parents or guardians in language that is understandable to them. The patients must be made aware of alternative therapies, if such exist, and that participation is voluntary. It has to be made very clear that failure to participate or withdrawal of consent will not result in any penalty or loss of benefits to which the patient is otherwise entitled. Patients must be provided with specific information about any costs associated with participation in the protocol, if such costs are not covered by the investigators or the involved institution. An accurate description of the possible benefits must be given, and the patients must be informed if no clinical benefit is expected. Possible risks, discomforts, and side effects must be presented including the possibility that unforeseen risks could occur. The prospective patients should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study, and they should be informed that any significant findings resulting from the study will be made known in a timely manner. Patients should be alerted that the media may have an interest in the innovative character of the protocol, and in the status of the treated patients. It should be indicated what measures will be taken to protect the privacy of the patients and their families. It may be necessary to maintain the confidentiality of research data in cases where data could be linked to individual patients.

In summary, the RAC review process requires three major elements: the research proposal

itself; a detailed response to the questions posed in the Points to Consider; and the informed consent document. The membership of the RAC has the appropriate diversity to address the above issues. Of the twenty five members, sixteen are scientists, and nine are "public" members who have expertise in such fields as law, ethics and public policy.

Current Status of Gene Therapy Protocols

As of September 1994, 90 protocols have been approved by the RAC. While the initial supposition was that gene therapy would be used primarily for genetic deficiency diseases, it turns out that the solid majority of the protocols (63) involve the study of cancer. Another six protocols were designed for the study of AIDS. Of the single gene deficiency diseases, there are ten protocols for the study of cystic fibrosis, three protocols for the study of Gaucher disease, a lipid storage disorder, and single protocols for the study of the following: adenosine deaminase deficiency type of severe combined immune deficiency; familial hypercholesterolemia, a disease that leads to very premature atherosclerosis; alpha-1-antitrypsin deficiency of the lung, which manifests itself by emphysema of the lung and cirrhosis of the liver; Fanconi's anemia, a condition characterized by very low blood counts and a predisposition to develop cancer; and Hunter syndrome, a storage disease that affects subcomponents of a cell, causing heart, lung and brain disorders. Other novel uses of gene therapy have involved inserting genes to modulate the inflammatory process in the joints of patients with rheumatoid arthritis, and a proposed treatment of peripheral artery disease using a gene that codes for a product that stimulates the growth of small blood vessels around a site where the artery is partially occluded. Almost all of the cancer protocols and many of the protocols for study of genetic deficiency diseases have used retroviral vectors for gene delivery. Nine of the protocols for study of cystic fibrosis have used adenoviral vector for gene delivery and one proposes to use the adeno-associated virus.

Several different approaches have characterized the study of various types of cancer. One of the most important findings involves the use of gene transfer technology to investigate bone marrow transplantation in the treatment of various types of leukemia and neuroblastoma. When matched bone marrow transplants are unavailable, patients frequently have been treated with their own bone marrow. Although this marrow is harvested during periods of clinical remission, there has always been some concern that it might contain malignant cells. When patients relapse following bone marrow transplantation, it has not been clear whether the recurrent disease had its origins in the bone marrow or in remaining malignant cells in other parts of the body. As a result of gene transfer studies of bone marrow cells, using the neomycin resistance gene, it has been possible to detect gene-marked cells when recurrent disease was detected. As a result of these findings, new methods of purging the bone marrow are being tested to help assure that malignant cells can be removed from the transplant.

A number of the cancer protocols have been designed to take advantage of what has been called adoptive immunotherapy, and there have been two general lines of approach. One involves the modification of immune cells to stimulate the patient's immune function, and

the other involves modification of the patient's own malignant cells to create immune recognition and rejection. In the first type of approach, cytotoxic T cells, so-called tumor-infiltrating lymphocytes, have been isolated directly from the tumor and the gene coding for a cytokine, such as interleukin-2, has been inserted into such cells before they are returned to the patient. In the second approach, the patient's tumor cells are transduced with either the interleukin-2 gene or the tumor necrosis factor gene with the goal of boosting immune recognition of these cells. Although these approaches to cancer therapy remain to be proven effective in patients who are in the advanced stages of their disease, it is entirely possible that adoptive immunotherapy will prove to be useful as an adjunct treatment that helps slow progression of disease.

Another interesting methodology has been developed for use in treatment of brain tumors. The herpes simplex virus thymidine kinase (HS-TK) gene has been inserted into a mouse cell line, using a retroviral vector. Through the use of stereotactic surgical procedures, these mouse cells are directly injected into the tumor site or the site where tumor has been removed. Since normal brain cells are non-proliferating, the only selective incorporation of the HS-TK gene construct occurs in the actively proliferating tumor cells. Those tumor cells containing the HS-TK gene are now uniquely sensitive to the antiviral drug, ganciclovir. Ganciclovir is administered to the patients seven days after the mouse producer cells are placed in the brain. At its most recent meeting, the RAC approved a modification of this approach to treating brain cancer; this new protocol proposes the insertion of the HS-TK gene into an adenovirus vector instead of mouse cells, and has a possible advantage in that there is no introduction of a foreign protein (mouse cells) into the brain of the patient.

In the several protocols approved for the study of AIDS, a variety of approaches are being pursued. One involves the use of gene transfer to induce an immune response in AIDS patients. The gene construct consists of a mouse retrovirus containing the gene coding for the human immunodeficiency virus (HIV) envelope protein, IIIB. Preliminary animal studies have demonstrated that such a system could stimulate cytotoxic lymphocyte and antibody responses; it is hoped that similar responses can be evoked in humans with AIDS and that both HIV-infected cells and cell-free virus can be eliminated in these individuals.

Another strategy is to interfere with the cycle of HIV replication; the HIV-1 Rev protein facilitates the appearance of unspliced viral messenger RNAs and plays a role in the regulation of viral latency. By creating a mutated form of the REV gene, a defective protein is produced that acts as an inhibitor of HIV. The mutated form of REV will be inserted into a patient's CD4+ lymphocytes, these lymphocytes will be returned to the patient, and the survival of the cells will be measured as compared to controls.

Another methodology for inhibiting HIV replication will require the use of a ribozyme, an RNA molecule that contains anti-sense sequences. This ribozyme interferes with two separate steps in the virus life cycle, cleaving both viral RNA and viral messenger RNA. The patient's CD4+ lymphocytes will be treated with a retroviral vector that contains the ribozyme, and the survival of these treated cells will be studied with the goal of aiding the

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design of future trials that can be done on a larger scale.

The use of gene-modified cytotoxic T lymphocytes in HIV-infected identical twins may yield important information about ways to treat AIDS patients. White blood cells called CD8+ T cells kill cells infected with viruses and are an important component of the body's defense against viral infections. Although CD8+ cells play an important role in temporarily controlling HIV infection, data suggest that a breakdown of the cell response may be responsible for the progression to AIDS. Genes have been inserted into CD8+ T cells so that they will be able to specifically recognize HIV-infected cells and kill them. In the planned clinical study, CD8+ T cells will be removed from an uninfected identical twin of an HIV-infected patient and genetically modified. The genetically modified cells will be purified and expanded to large numbers in the laboratory before infusion into the HIV-infected twin patient. By monitoring immune status, viral burden, organ function, and persistence of the cells in the body, it is hoped to determine if this potential therapeutic approach is feasible and safe.

Despite the diversity of diseases that are targets for genetic intervention, most all of the protocols seen to date share a common feature in that these are early trials and the principal types of information to be derived will include safety, tolerance for the procedures, and expected and unexpected toxicities. Although therapeutic benefits possibly may be observed, they cannot be construed as the primary goal for these so-called Phase I studies. The patient base is relatively modest; the latest publicly available figures indicate that a total of 219 patients have been entered into the active protocols. While the rapid developments in the field are encouraging, many scientific and technical problems still require solution.

NIH Support of Human Gene Therapy Research

There are a number of different types of commitments made by the NIH in its support of human gene therapy. One of the most important involves the support of investigator-initiated grants, the so-called R01 grants, in the fields of molecular biology and genetics. The developments in the study of transgenic mice, the creation of single gene mouse models for human genetic disorders through the use of "gene knockouts," and the increasing sophistication in the micromanipulation of embryos are all of critical importance. It should be emphasized that this work in animal models is absolutely necessary as a prologue to doing human experimentation. It is a more judicious use of resources to establish the validity of an experimental approach in model systems, and it can prevent the premature introduction of clinical trials that may have little real chance of success.

The Human Genome Project is highly complementary to the efforts in human gene therapy. It has been estimated that this project will be completed by the year 2005, at which time the estimated 100,00 human genes will have been sequenced. While many of the mutations that cause the single gene deficiency diseases are identified, one of the most encouraging outcomes that will derive from the Human Genome Project is the capacity to identify genes

that contribute to multifactorial diseases such as atherosclerosis and cancer.

Fourteen institutes and centers have committed resources specifically for the support of gene therapy, including grant and program project support for extramural research, and support for intramural research. Participating entities include: National Cancer Institute; National Heart Lung and Blood Institute; National Institute of Dental Research; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Neurological Disorders and Stroke; National Institute of Allergy and Infectious Diseases; National Institute of General Medical Sciences; National Institute of Child Health and Human Development; National Institute on Aging; National Institute of Mental Health; National Institute of Environmental Health Sciences; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Center for Human Genome Research; and National Center for Research Resources.

It is of particular interest to gene therapy research that the General Clinical Research Centers program exists. This is a national network of 75 centers that are configured as geographically discrete areas within the hospital of an academic medical center. Investigators who use these centers are funded by other components of NIH and by Federal, state and local agencies. Such centers are resources for multidisciplinary research such as gene therapy and there are specialized laboratories and inpatient facilities to accommodate the type of patient population that gene therapy patients represent. Several of the centers have been used to study patients in active gene therapy protocols.

The Office of Technology Transfer has facilitated the development and implementation of Cooperative Research and Development Agreements (CRADAs) between NIH intramural scientists and private-sector biotechnology companies. The very first protocol for the treatment of adenosine deaminase deficiency represents this type of collaborative arrangement. Much of the vector/gene production was done on site at the biotechnology company, and the study of patients was done at the NIH Clinical Center.

Consolidated Review of Human Gene Transfer Protocols

During the past four years, the NIH and the FDA have conducted parallel but independent review processes; NIH reviews have been conducted in public and FDA reviews have been conducted in private, given the requirement for the latter agency to protect proprietary information. On July 18-19, 1994, the National Task Force on AIDS Drug Development held an open meeting for the purpose of identifying barriers to AIDS drug discovery that included a proposal to streamline the dual review process for human gene therapy experiments. Members of the Task Force recommended a consolidated review process to allow the NIH RAC to selectively review protocols. As a result of the Task Force deliberations, recommendations were adopted in order to eliminate any unnecessary overlap between the NIH and the FDA in their review of human gene therapy protocols. Both Drs. Varmus and Kessler noted that their respective agencies would cooperate fully to effect the changes necessary to implement these recommendations. At its meeting on September 12-

13, 1994, the RAC approved in concept the suggested changes in the review process. The specific recommendations for the consolidated review process are as follows:

The NIH and FDA recommend that the RAC become advisory to both the NIH Director and the FDA with regard to the review of human gene transfer protocols. In the interest of maximizing the resources of both agencies and in simplifying the method and period of review of research protocols involving human gene transfer, it is planned that the FDA and NIH initiate a new consolidated review process that incorporates the following principal elements:

(1) All gene transfer protocols shall be submitted directly to the FDA. FDA will modify its guidance documents to include the request for a response to the Points to Consider (Appendix M of the *NIH Guidelines)* before an IND submission.

(2) Upon receipt, FDA review will proceed. Staff members of the Office of Recombinant DNA Activities (NIH), members of the RAC, and FDA staff will decide on the necessity for full RAC review. The response to the Points to Consider will be publicly available for all human gene transfer submissions even if RAC review is not required.

(3) Factors which will define the need for RAC review include: (1) use of new vector systems, (2) targeting of new diseases for study, (3) unique applications of gene transfer, and (4) ethical issues that require further public review.

(4) Whenever possible, principal investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required.

(5) Semi-annual data reporting procedures will remain the responsibility of NIH (ORDA). Semi-annual data reports will be reviewed by the RAC in a public forum.

(6) RAC/FDA will broaden their scope of review in gene transfer to jointly and prospectively address global issues beyond the scope of individual protocol review, e.g., ethics and implementation of a gene therapy patient registry, access for "orphan" genetic disease patients to therapies, criteria for prenatal gene therapy, and transgenic technology for xenotransplantation.

Representatives of the NIH and the FDA are continuing to work on the implementation of this new review proposal with the goal of having the plan operational by the end of calendar year 1994.

Gene Therapy - Prologue to the Future

Human gene therapy research has been the subject of intense scrutiny by the press, and commissioned polls suggest that a majority of those interviewed are in favor of the use of

gene transfer techniques for the treatment of disease. Despite the early enthusiasm, certain caution is in order. The scientific infrastructure for this form of technology is in its early formative stages. A number of fundamental problems need to be addressed. As it currently exists, gene therapy is a high technology treatment that is limited to a few medical centers. It is labor intensive and requires a molecular biology laboratory, and people with expertise in virology to prepare vectors. Many quality control and safety assays are mandatory. Required hospital facilities include an intensive care unit or a bone marrow transplantation unit, or an isolation facility if there is concern about horizontal spread of the virus vector.

There are at least three developments that are critical to the future progress of gene therapy. First, there is the necessity to develop injectable, targetable vectors, vectors that can reliably migrate to a specific organ site. Our current methods of inserting genes in an *ex vivo* fashion are cumbersome to say the least; removing cells from the body, treating such cells with retroviruses containing exogenous genes, and then expanding those cells exponentially in a culture system before returning them to the patient is unwieldy and subject to the hazard of contamination by adventitious bacterial or viral agents.

Second, it will be important to develop methods that allow for reliable site-specific integration of genes. With the rather extensive use of retroviral vectors, it is possible to produce a fairly efficient transfer of genes into a variety of cells, but the integration sites are random and this makes insertional mutagenesis a low but continuing risk for the development of cancer, particularly where treatment for a disease may have to be repeated on multiple occasions. When genes can be repetitively inserted at a single site that does not impair normal gene function, activate an oncogene, or inactivate a tumor suppressor gene, then gene therapy will be relieved of one of its current risks.

Third, there is the regulation of gene expression by physiological signals that will have to be addressed as this field progresses. At present, gene therapy protocols are designed to simply add a gene that will produce a gene product at sufficient levels and for a sufficient period of time to have some effect on the disease state. In order to regulate gene expression, we may be required to program gene-treated cells to respond to physiological changes, such as in the treatment of diabetes. Our knowledge regarding mechanisms of gene regulation is still in a relatively rudimentary stage.

In summary, gene therapy is in its early stages and it is not likely that any commercial products will be available for several years. Data on efficacy is yet to be seen. There have not even been any requests for Phase II trials. While gene therapy remains highly experimental, there is every reason for optimism, and it is already apparent that its utility is not limited to genetic deficiency diseases. If effective treatments for cancer, cardiovascular disease and AIDS can be developed, and if gene delivery systems can be refined, the expense of this type of intervention is probably justifiable, particularly when the costs of the major categories of disease are considered in the context of disability, absence from work, decreased productivity, abnormal shortening of life span, and the use of treatments that are palliative at best. I would be happy to answer any questions.

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BILLING CODE 4710-20-M

OFFICE OF SCIENCE AND TECHNOLOGY

National Bioethics Advisory Commission Proposed Charter

AGENCY: Office of Science and Technology Policy (OSTP).

ACTION: Request for Comments.

SUMMARY: This notice describes a proposal to establish a National Bioethics Advisory Commission within the Executive Branch. The Commission would be charged to consider issues of bioethics arising from research on human biology and behavior, and the applications of that research.

DATES: Comments must be received on or before October 11, 1994.

ADDRESSES: Submit written comments by mail to: Bioethics Docket, Office of Science and Technology Policy, Room 436, OEOB, Washington, D.C. 20500, or by FAX to: 202–456–6027.

FOR FURTHER INFORMATION CONTACT: By mail: Rachel E. Levinson, Assistant Director for Life Sciences, Office of Science and Technology Policy, Room 435, OEOB, Washington, D.C. 20500. Office telephone number: 202–456–6137.

SUPPLEMENTARY INFORMATION: OSTP proposes that a standing advisory body be established within the Executive Branch to consider issues of bioethics arising from research on human biology and behavior, and the applications of that research. This action would fulfill a need recognized by all branches of the Federal government. For example, a report by the House of Representatives Committee on Government Operations recommended establishment of an advisory committee to examine the ethical, legal and social implications of the Human Genome Project. The proposed advisory body would expand the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; the Department of Health, Education and Welfare's Ethics Advisory Board; and the President's Commission for the Study of Ethics Problems in Medicine and Biomedical and Behavioral Research.

OSTP seeks comments on a draft charter for a proposed National Bioethics Advisory Commission (NBAC). The NBAC would report to the President's National Science and Technology Council (NSTC). This arrangement will facilitate access to the deliberations and recommendations of the NBAC for the Executive Branch agencies most heavily invested in biological and behavioral research.

The Commission would be asked to identify and develop broad overarching principles to govern the ethical conduct of biological and behavioral research, and the applications of that research. The proposed NBAC would not have responsibility for the review and approval of individual projects.

The draft charter seeks to strike a balance between defining the NBAC's agenda so as to fulfill governmental needs, and allowing the Commission sufficient flexibility to advise the government on issues this group of experts and stakeholders believe should be addressed.

The charter specifies two prospective areas of inquiry, issues in the management and use of genetic information, and protection of the rights and welfare of research subjects. Discrete issues that fall under these two broad topics include issues of genetic privacy, screening for genetic disorders, intellectual property rights, access to research data or materials developed with public funding, current views on informed consent, adequacy and implementation of Federal human subject research guidelines, and the concept of "minimal risk."

In addition, several other potential issues for consideration by the Commission have been raised in discussions to date including adequacy and implementation of Federal human subject research guidelines, recommendations on requirements to maintain research data, and the ethical aspects of access to costly health care technology. The question is, how best might the scope of the Commission's charge be defined so as to meet public needs for deliberation of pressing issues in bioethics, without being so broad as to limit its effectiveness? An alternative option for addressing the last issue, for example, might be referral to a body more directly involved with decisions related to the provisions of health care and relevant cost/benefit analysis.

The Commission would be established in accordance with the Federal Advisory Committee Act (FACA). As such, its meetings would be open tot be public and announced in advance to facilitate public participation. In addition, reports produced by the NBAC would be made available to public either *in toto*, or in summary. The purpose of these efforts would oe to involve the public in the deliberations of the NBAC to the greatest extent possible.

As a FACA committee, the NBAC will be required to have a balanced membership. Naturally, selection of Commission members is going to be a delicate process that should take into account the social and cultural mores of the times in order to establish a body that is sensitive to the potential impacts of its deliberations and recommendations. The draft charter proposes that members be appointed by the President. Suggestions for potential members or membership posts are sought through this Notice.

Draft Charter

Proposed National Bioethics Advisory Commission

Purpose

The National Bioethics Advisory Commission will provide advice and make recommendations to the National Science and Technology Council, other appropriate entities and the public, on bioethical issues arising from research on human biology and behavior, and the applications of that research.

Authority

42 U.S.C. 6617(a)(2). This Commission is governed by the provisions of the Federal Advisory Committee Act (FACA), Public Law 92–463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation of advisory committees, and implementing regulations (41 CFR 101–6.10).

Functions

The National Bioethics Advisory Commission shall advise, consult with, and make recommendations to the National Science and Technology Council and other appropriate entities, and also make their advice and recommendations available to the public. The Commission's purview includes the appropriateness of departmental, egency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior, and applications of that research. The Commission shall identify broad, overarching principles to govern the ethical conduct of research, citing individual projects only as illustrations for such principles. The Commissiono shall not be responsible for the review and approval of individual projects.

As a first priority, the Commission will direct its attention to consideration of:

A. Issues in the management and use of geoetic information; and

60 day comment period.

B. Protection of the rights and welfare of research subjects.

In receiving and responding to requests for advice and recommendations from the National Science and Technology Council, the Commission shall consider four criteria in establishing priority for its activities:

A. The public health or public policy urgency of the bioethical issue.
B. The relation of the bioethical issue to the goals for Federal investment in science and technology.
C. The absence of another body able to fruitfully deliberate on the bioethical issue.
D. The extent of interest in the issue across the government. (The Commission ordinarily will not deliberate on a bioethical issue of interest to just one department or agency.)

The Commission also shall have the authority to identify bioethical issues, on its own behalf, for deliberation. The Commission will accept suggestions of issues for consideration from Federal agencies, Congress and the public. The Commission's decision to deliberate on a specific topic shall be made in consultation with the National Science and Technology Council. In all such instances, the four stated criteria for establishing priority shall pertain.

Structure

The National Bioethics Advisory Commission shall consist of not more than 15 members, including the Chairperson. Appointments shall be made by the President, who shall select from knowledgeable non-Government experts and community representatives with special qualifications and competence to deal effectively with bioethical issues of concern to the participating departments and agencies. At least one member shall be selected from each of the following categories of primary expertise: (i) bioethics/theology; (ii) social/behavioral science; (iii) law; (iv) medicine/allied health professions; and (v) biological research. At least three members shall be selected from the general public, bringing to the Commission expertise other than that listed. The membership shall be approximately evenly balanced between scientists and non-scientists.

Members shall be appointed for overlapping four-year terms. Initially, members will be appointed for two-, three- or four-year terms. Terms of more than two years are contingent upon renewal of the National Bioethics Advisory Commission by appropriate action prior to its termination. The Chairperson shall be appointed by the President. The term of office for the Chairperson shall be two years, renewable by appropriate action of the President.

If a vacancy occurs on the Commission, the President shall make an appointment to fulfill the term. Any member appointed to fill a vacancy occurring prior to expiration of the term for which his or her predecessor was appointed shall serve for the remainder of such term. Members may serve after the expiration of their terms until their successors have taken office.

The Commission may conduct inquiries, hold hearings and establish subcommittees, as necessary.

The Commission is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on the Commission, the Commission is also authorized to contract for the services of non-governmental consultants who may conduct analyses, prepare reports and background papers or prepare other materials for consideration by the Commission, as appropriate.

In order to avoid duplication of effort, the Commission may, in lieu of, or as part of any of its authorized activities, incorporate the results of the deliberations of another entity as long as the Commission sets forth its reasons for doing so.

The Assistant to the President for Science and Technology shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration of the subcommittee, and estimated frequency of meetings.

Management and support services shall be provided by the Office for Protection from Research Risks, Department of Health and Human Services. Additional resources including, but not limited to personnel, office support and printing will be provided by other NSTC member agencies.

Meetings

Meetings of the Commission shall be held up to 10 times a year at the call of the Chairperson with the advance approval of a Federal Government official who shall also approve the agenda. Meetings of the subcommittee(s) shall be convened as necessary. A Federal Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Assistant to the President for Science and Technology. Advance notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of proceedings kept, as required by applicable laws and Federal regulations.

Compensation

Members may be compensated at a rate not to exceed the maximum pay authorized by 5 U.S.C. 3109, plus per diem and travel expenses as in accordance with standard government travel regulations.

Annual Cost Estimate

The estimated annual cost for operating the National Bioethics Advisory Commission, including compensation and travel expenses for members and contracting and publication services costs, but excluding that for staff support, $1,500,000. The estimated annual person years of staff support is six, at an estimated annual cost of $500,000.

Reports

Reports by the National Bioethics Advisory Commission on specific issues shall be submitted to the National Science and Technology Council, the appropriate committees of Congress, and other appropriate entities. The Commission may specifically identify the Federal department, agency or other entity to which particular recommendations are directed and request a response from the Federal department, agency or other entity within 180 days of publication of such recommendations.

Executive summaries of each report of the Commission shall be promulgated in the Federal Register. Such summaries shall specifically list the department, agency, or other entity to which any recommendations are directed and the date by which such responses are expected.

An annual report shall be submitted to the National Science and Technology Council and the appropriate committees of Congress. It shall contain, at a minimum, (i) the Commission's function; (ii) a list of members and their business addresses; (iii) the dates and places of meetings; (iv) a summary of the Commission's activities during the year; (v) a summary of the Commission's recommendations made during the year; and (vi) a summary of responses made by departments, agencies, or other entities to the Commission's recommendations during the year.

Termination Date

Unless renewed by appropriate action prior to its expiration, this National Bioethics Advisory Commission will

terminate two years from the date this charter is approved.

Barbara Ann Ferguson,

Administrative Officer, Office of Science and Technology Policy.

[FR Doc. 94-19688 Filed 8-11-94]

BILLING CODE 3170-01 OSTP-M

DEPARTMENT OF TRANSPORTATION

Office of the Secretary

Criteria and Application Process for the Secretarial Award for Excellence in Transportation Technology Research and Development

AGENCY: Department of Transportation, Office of the Secretary.

ACTION: Notice of Request for Nominations.

SUMMARY: The Department of Transportation (DOT) announces procedures for nominating individuals and organizations for the Secretarial Award for Excellence in Transportation Technology Research and Development. Awards are made annually by the Secretary of Transportation to recognize research and development contributions advancing the ability of the U.S. transportation industry to compete globally.

DATES: Nominations must be postmarked no later than October 30,1994.

ADDRESSES: An original and three copies of the nomination should be sent to: Noah Rifkin, Director of Technology Deployment, Office of the Secretary, U.S. Department of Transportation, 400 7th Street, SW, Washington, DC 20590, Room 10200.

FOR FURTHER INFORMATION CONTACT: John E. Hohl, Technology Sharing Officer, Research and Special Programs Administration, U.S. DOT 400 7th Street, SW, Washington D.C. 20590 Telephone. (202) 366-4978

SUPPLEMENTARY INFORMATION:

Background

This notice solicits nominations for the Secretarial Award for Excellence in Transportation Technology Research and Development and provides relevant information on the nomination and selection process. The award is honorary recognition in the form of a certificate from the Secretary of Transportation. Awards will be presented annually.

Purpose

DOT is committed to providing the nation with a safe, efficient, environmentally sound and technologically advanced transportation system that promotes economic growth, enhances international economic competitiveness, and contributes to a secure and healthy environment. In fulfilling this mission, the Department intends to accelerate technological advances that promote the development and export of transportation technology and manufactured products. To further these goals, the Secretary of Transportation has established the Secretarial Award for Excellence in Transportation Technology Research and Development to recognize significant contributions to expanding the technology knowledge base and the ability of the transportation industry to compete internationally.

Organization Defined

- For purposes of this award, organizations include but are not limited to:
- Domestic or U.S. Corporations, including nonprofit corporations,
- Partnerships;
- Professional associations;
- Institutions of higher education,
- Federal, State, or local government, and
- Professional teams assembled for the specific projects.

Evaluation Criteria

Nominations will be evaluated based on the following criteria:

- Quality and innovative nature of the technology developed;
- How the technology has enhanced industry competitiveness, both domestically and internationally.
- Significance of individual or organization nominated to the success of the development effort
- Entrepreneurial nature of research effort (nature of collaboration);
- Potential for positive economic benefits to the U.S. or specific region; and
- Applicability to more than one mode of transportation.

The qualifying work may be a singular accomplishment or a series of accomplishments that have had a substantial effect over time. Generally, technologies applicable to more than one transportation mode will be more favorably considered.

Examples of achievements that may be recognized include but are not limited to:

- Safety Improvements—Technology that reduces the likelihood of vehicle accidents or the likelihood of serious injury when a vehicle accident does occur or otherwise improves the chances of post-accident survival/recovery of accident victims. This could include research and development of instrumentation equipment, human factors, or biomechanics.
- Energy Savings.—Technology that saves energy in the production, operation, or disposition of vehicles through research in materials development, alternative fuels, engine and propulsion modifications, aerodynamic modeling and drag reduction, and combustion research
- Environmental Quality—Technology applicable to transportation that reduces emissions; hazardous, solid or toxic waste; noise. This could include research and development of products, processes, or measurement instrumentation.
- International Industrial Competitiveness—Technology that allows the U.S. transportation industry to achieve sustainable world-class capabilities to compete in the global marketplace through the sale of transportation vehicles and equipment in oversees markets or the provision of freight and passenger transportation services to support international trade and travel.
- Job Creation—Transportation technology that creates jobs and makes a positive contribution to the U S economy.

Evaluation Process

The DOT Research and Technology Coordinating Council, chaired by the Director of Technology will appoint an Evaluation Committee to evaluate nominations under the prescribed criteria and to recommend awardees.

Recommendations of the Evaluation Committee will be reviewed by a Selection Committee made up of members of the Research and Technology Steering Committee. Final selections will be made by the Secretary of Transportation.

Nominating Procedures

Any person may nominate individuals or organizations from industry, academia, or government. Nomination should be in the form of a letter and must demonstrate that the nominee has provided significant contributions, through technology research and development, to advancing the ability of the U.S. transportation industry to compete globally in an area of transportation systems development, vehicle or facility design, construction, operation, or maintenance. Nominations must include the following:

- Name and address of the individual or organization being nominated;
- Name, address, and telephone number of the nominator. If the

INTRODUCTORY REMARKS

Dr. Wivel is Director of the Office of Recombinant DNA Activities at the National Institutes of Health. It is his responsibility to ensure that NIH supported research projects will be conducted in compliance with the NIH Guidelines for Research Involving Recombinant DNA Molecules. The Guidelines are applicable to all NIH-supported recombinant DNA research conducted at universities and research institutes as well as the intramural program located on the campus in Bethesda.

Prior to assuming this position, Dr. Wivel was active in the intramural research program at NIH for 20 years where he was Head of the Ultrastructural Biology Section in the National Cancer Institute. His research in molecular biology focused on the murine retroviruses and his research group was one of the first to identify a mammalian retrotransposon. Another primary research effort involved a study of the effects of interferon on the replication of retroviruses, and the results observed in a mouse model system were later used as a basis for developing an interferon treatment program for AIDS patients.

Dr. Wivel has served as an Associate Editor of the Journal of the National Cancer Institute, and he is a member of the American Society for Virology and the American Society for Cell Biology. He is a graduate of the Stanford University School of Medicine and completed a residency in pathology, followed by postdoctoral training in molecular virology.

The CHAIRMAN. Thank you very much, Doctor.

Dr. Noguchi, did you have a statement that you wanted to make, or are you just here to monitor Dr. Wivel?

Dr. NOGUCHI. Mr. Chairman, I would appreciate the chance to offer a new comments from the FDA's perspective.

The CHAIRMAN. We would be happy to have your testimony.

Dr. NOGUCHI. Thank you very much, and thank you and the committee for allowing FDA this opportunity.

I just want to briefly go over a couple of general questions that people often have. For example, what is the FDA's role in the regulation of gene therapy?

Now, in general, the FDA derives its regulatory oversight by promulgation of regulations based on the Food, Drug, and Cosmetic Act as revised and Section 351 of the Public Health Service Act. In 1986, FDA did declare that gene therapies would be considered to be a biological product and that they would be subject to licensure by FDA under Section 351. The lead center is the Center for Biologics Evaluation and Research, and is responsible not only for gene therapies but for other biotechnology products as well. Some of their previous examples of the early licensed biologicals include some antitoxins and the smallpox vaccines, mumps, measles, rubella and polio in the 1950s and 1960s, and more recently, a number of biotechnology products.

Prior to the revolution in biotechnology, most of our products were viral or bacterial vaccines, blood or blood products or allegenic extracts. But in the past six years, CBER has responded to the rapid growth in biotechnology by forming four new product division.

In 1988, the Division of Cytokine Biology responsible for some of the first approvals for Interferons and interleukins, and then in 1993, a separate division to address monoclonal antibody concerns, hematologic products, which includes thrombolytics and erythropoietins, and the Division of Cell and Gene Therapy. And this last division has the lead role in regulating both cell and gene therapies.

Now, specifically for gene therapies, investigational clinical trials in humans are subject to general requirements of the FD&C Act as codified in Title 21, specifically Section 312. This includes investigational new application which has a number of new requirements including extensive documentation of methods of production and preclinical testing.

At this point in time, over 70 INDs for human gene therapy have been submitted to the agency and about one-third of those have actually been submitted within the last 10 months. All of these we consider to be Phase I safety studies only.

Again, in general, as these types of products were moved from Phase I through Phase II and Phase III, other portions of the 21 CFR will apply, such as the 300 series on new drug application, the 600 series on biologic establishments and licensing, and this level of regulation is actually the same for all biological products that are considered to be drugs. And they focus on safety, purity and efficacy.

Now, it should also be noted, however, that from FDA's perspective, human gene therapy represents the publicly visible portion of

an extremely rapid evolving medical revolution. Gene therapies could not be contemplated without the ready availability of purified cytokines to allow expansion and differentiation of cells. Likewise, monoclonal antibody technology has allowed the purification of a variety of cells from tissues which can then be transduced in vivo.

Investment by the NIH in basic biomedical research studies created the ability to isolate medically relevant genes and to create the vectors that are used in gene therapy. The clinical arena involving organ tissue and cell transplantation have provided the means for ex-vivo manipulations and portend the future use of transgenic animals carrying human genes for xenotransplantation.

Even the medical device area is rapidly entering the field with both extracorporeal as well as implantable devices that are being examined as delivery systems for human gene therapy.

Four years is a relatively short time for a new clinical field and, in truth, we have only seen the very simplest approaches to gene therapy. Although the future will bring exponential complexity to our goal of improving and protecting the public health, the broad authorities of the FDA, including the recently enacted ones for device regulation, will allow the FDA to responsively regulate this area.

And if I might just take an additional moment to address the specific interactions with the RAC committee. Now, over the past four years, the RAC and the FDA have interacted on a closer and closer basis. The RAC meetings from FDA's point of view allow for public discussion of both the accomplishments as well as the adverse findings that are associated with gene therapy.

Because these meetings are public, the discussions of safety concerns can be immediately communicated to the entire industry and a consensus to resolve the issues can be reached that would otherwise be very difficult to obtain because of our restriction on secret regulations.

In addition, the evolution of RAC oversight to prospectively discuss these emerging issues is obviously going to be of increasing importance. I would like to give one example which will illustrate how the RAC process has enlarged FDA's overall role.

For example, in June of last year, one of the patients—first patients treated for gene therapy for cystic fibrosis developed an adverse reaction which was immediately communicated to both the FDA and the RAC. Because the public nature of gene therapy protocols is widely known, both the FDA and the RAC communicated this to other investigators and we were able to continue all the studies at reduced levels of dosing without having to shut any of them down. And without having to really do anything out of the ordinary in terms of FDA oversight.

Now, advances in product development are based not only on positive or encouraging results but also on the knowledge that is gained from approaches that have undesirable toxicities. As a result the Cystic Fibrosis Foundation sponsored a three-and-a-half day meeting on gene therapy in which 10 FDA individuals cochaired a number of breakout sessions that focused on quality control and product development issues.

These sessions have led to a development of a variety of new approaches to gene therapy of cystic fibrosis including new genera-

tions of viral vectors, other viral and nonviral approaches. We feel it is likely that the diversity of approaches that we have recently seen was greatly accelerated by the early knowledge that adenoviral vectors could have unwanted toxicity.

Now that has has been established that the principles of gene therapy can be established in, quote, unquote, "trials," we feel that it is very prudent to refocus the public discussions in a prospective manner. And we believe that the recent proposals endorsed by the RAC, by the NIH and FDA serve as a blueprint to achieve that goal.

Thank you very much.

[The prepared statement of Dr. Noguchi follows:]

1. What is FDA's role in the regulation of gene therapy?

The Food and Drug Administration (FDA) derives its regulatory oversight by promulgation of regulations based on the Food, Drug and Cosmetic Act (revised) (FD&C Act) and Section 351 of the Public Health Service Act (PHS Act). In 1986, FDA announced that gene therapies would be considered to be biological products subject to licensure by FDA under section 351 of the PHS Act. The Center for Biologics Evaluation and Research (CBER) is currently responsible for the regulation of the manufacturing and labeling of biologic products. Examples of the earliest licensed products in the 1900s include antitoxins and the Smallpox Vaccine, and vaccines for viral diseases such as mumps, measles, rubella and polio were licensed in the fifties and sixties.

Prior to the revolution in biotechnology, most biologic products were either viral or bacterial vaccines, blood or blood products or allergenic extracts. CBER has responded to the rapid growth in biotechnology by forming four new product divisions, including in 1988, the Division of Cytokine Biology and in 1993, three Divisions including Monoclonal Antibodies, Hematologic Products and the Division of Cellular and Gene Therapies. This last division has the lead role in regulating gene therapy.

Investigational clinical trials in humans with gene therapy products are subject to the general requirements for drugs and biologics in Title 21 of the Code of Federal Regulations (CFR). This includes 21 CFR Part 312, the Investigational New Drug Application (IND) which has a number of requirements, including extensive documentation of methods of production and preclinical testing. Over 70 INDs for human gene therapy have been submitted to the Agency, with about 1/3 of those submitted in the last 10 months. All of these have been phase 1 safety trials.

In general, as products move from phase 1 thru phase II and phase III, other portions of the 21 series pertain, including the 200 series on Current Good Manufacturing Practices (GMPS), the 300 series on new drug applications, the 600 series on biologics establishments and licensing. This level of regulation is the same for all biological products that are considered to be drugs, and focus on safety, purity,

potency and efficy considerations.

It should be noted, however, that from the FDA's perspective, human gene therapy also represents the publicly visible portion of a rapidly evolving medical revolution. Gene therapies could not be contemplated without the ready availability of purified cytokines to allow expansion and differentiation of cells. Likewise, monoclonal antibody technology has allowed the purification of a variety of cells from a number of tissues that can then be transduced with vectors. The investment by NIH in basic biomedical research studies has created the ability to isolate medically relevant genes and to create the vectors used in gene therapies. The clinical arena involving organ, tissue and cell transplantation have provided the means for ex-vivo manipulations, and portend the future use of transgenic animals carrying human genes for xenotransplantation. Even the medical device field is rapidly entering the field of gene therapies. Both extracorporeal as well as implantable devices with human and nonhuman tissues are being examined as potential delivery systems for gene therapies, and the use of medical devices for isolating stem cells is rapidly growing.

Four years is a relatively short time for a new clinical field and we have only seen the simplest approaches in gene therapy. Although the future will bring exponential complexity to our common goal of improving the public health, the broad authorities of the FDA including recently enacted ones for device regulation will allow the FDA to responsibly regulate this area.

2. *How does the RAC assist and or enhance FDA's review of gene therapy?*

FDA and NIH's RAC have interacted on an increasingly frequent basis during the past four years. The RAC meetings allow for public discussion of both accomplishments and adverse findings associated with gene therapy. Because these meetings are public, the discussions of safety concerns can be immediately communicated to the entire industry and a consensus to resolve the concerns can be reached with industry that would otherwise be restricted by the trade-secret regulations. In addition, the evolution of RAC oversight to prospectively discuss emerging issues will serve an increasingly important role.

An instructive example of this process occurred in June, 1993. The RAC and FDA received notice of an adverse reaction in the third patient to participate in a gene therapy protocol for cystic fibrosis. Because of the public nature of gene therapy protocols, the RAC and FDA were able to communicate the details of this adverse event to other investigators. This allowed for appropriate modification of the protocol that allowed the trial to continue with close FDA oversight. Advances in product development are based not only on positive or encouraging results, but also on the knowledge gained from approaches that have undesirable toxicities. The Cystic Fibrosis Foundation sponsored a 3 and 1/2 day meeting on gene therapy, in which 10 FDA staff participated in cochairing breakout sessions that focused on quality control and product development concerns utilizing the data in the RAC public database. These sessions have led to the development of a variety of new approaches to gene therapy of cystic fibrosis, including new generations of adenoviral vectors, and other viral and nonviral approaches. It is likely that the diversity of approaches was greatly accelerated by the early knowledge that adenoviral vectors may have altered properties relative to the parent virus.

Now that it has been established that the principles of gene therapy can be examined in clinical trials, it is prudent to refocus the public discussions in a prospective manner. The recent proposals endorsed by the RAC, NIH and FDA serve as the blueprint to achieve that worthy goal.

Biographical sketch
Philip D. Noguchi, M.D.
Director, Cellular and Gene Therapies
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Philip D. Noguchi, M.D. is Director of the Division of Cellular and Gene Therapies (DCGT), Office of Therapeutics Research and Review (OTRR), Center for Biologics Evaluation and Research (CBER). After postgraduate training in pathology at the George Washington University Hospital, he became a Research Associate at CBER in 1975, and has served in a number of capacities at CBER for the past 19 years, including Chief of the Laboratory of Cellular and Molecular Biology and Deputy Director of the Division of Biochemistry and Biophysics. In addition to pursuing an active research program in human tumor biology, he has been involved in a number of regulatory issues involving sperm banking, tissue and cell transplantation, recombinant DNA and monoclonal antibody products, and cellular and gene therapies. He has been a member or chair of license committees for the first approved alpha interferons, original approvals of the monoclonal antibodies, OKT-3 and OncoScint, and erythropoietin. Dr. Noguchi received his A.B from the University of California at Berkeley and his M.D. from the George Washington University School of Medicine.

In his current role, Dr. Noguchi is responsible for directing the research efforts of the DCGT toward peer-reviewed risk assessment as well as development of technical standards for cellular and gene therapies. He is also responsible for developing guidance and policies for this burgeoning area. He serves as the Agency representative to the NIH Transplantation Coordinating Committee, the NIH Recombinant DNA Advisory Committee and the Task Force on Transplantation, National Kidney and Urologic Diseases Advisory Board.

The CHAIRMAN. Thank you very much, Dr. Noguchi. Your testimony was very impressive. I think that the future which you said would bring exponential complexity has already arrived here in terms of my understanding of all of your testimony.

Dr. Greenwood, we have a situation where the responsibility for research in this area, research and development, is split amongst a number of different and important government agencies. The Human Genome Project involves many agencies. I think, if I recall correctly, Health and Human Services and Energy were cochairmen of that activity but many others are involved.

Do you feel that the process at the top in the White House for properly coordinating all of this kind of research is working efficiently, or are there any improvements that you might want to suggest to this committee so that we could mess them up?

Dr. GREENWOOD. Mr. Chairman, thank you for asking that question. And I wouldn't predict that you would mess them up. But let me do tell you that I think that the process that we have put in place with the National Science and Technology Council, with which you are very familiar, most of the members are, is working very well to bring together the agencies across a series of issues, both the scientific opportunity issues and the issues related to the policy, the scientific basis of policy-making, and the issues related to the future of molecular biology and gene therapies are under active discussion in these committees, and there is a very excellent attempt to have the programs reinforce each other to work towards reducing redundancies.

I have been very pleased in the brief year that I have been in Washington with the level of discussion and the effective operation to try to coordinate some of these. Of course, it is not simple. And to suggest that top-down coordination, you know, from the highest levels of the administration, whatever they might be, would be the most effective way for stimulating ideas would also be a faulty assumption.

So I think it is important to keep the environment for discovery fertile and active. On the other hand, to get the best arrangements of coordination we can, I think we are doing a pretty good job with that right now.

The CHAIRMAN. We appreciate that evaluation. We have not had uniform success with cross-department coordination or cross-disciplinary coordination, and it does work best if there is a culture that supports it.

Can I ask Dr. Wivel and Dr. Noguchi to comment if they perceive that there is effective coordination at the working level?

Dr. WIVEL. I certainly can speak to our interactions with FDA and the matter of review of gene therapy, and I think we have both an effective and collegial relationship, and our goal is not to unnecessarily encumber the system but to promote it while protecting the safety of the people who participate and the public.

Dr. NOGUCHI. I would agree on that interaction. I think we have also jointly undertaken some initiatives that we hope will start to address some of the issues in terms of costs of production and so forth.

Since the RAC is a regularly scheduled meeting, the FDA has started to hold joint meetings in the evening in which members of

the academic and industrial community can actually hold discourse with the FDA on such issues as what level of GMP—that is Good Manufacturing Practices—are necessary for various degrees of investigation. Early in an investigation you may need less control than you do need later in the investigation and we hope that this will impact on the whole process.

The CHAIRMAN. It is our hope in this committee, which is the Science and Technology Committee, that the advance of technology will allow for the proliferation of local area, computer, and television networks that will make it seem like you were virtually in the same office, no matter where you were and that that would facilitate this kind of coordination. That may be an idle hope, but we still hope it will happen.

Mr. Valentine.

Mr. VALENTINE. Mr. Chairman, I have just a question or two I would like to ask Dr. Greenwood. This seems like an unimportant question when we see the young lady here who has been affected by all these advances, but these are questions that we for our purposes need to have your advice about.

What is the importance, in your opinion, of gene therapy for the competitiveness of the U.S. biochemical industry as a whole?

Dr. GREENWOOD. Well, I think the issue of what will constitute gene therapy for the future in the competitiveness sense and in the sense of industry is still for us to understand. I believe that this will be at some point in our future, a very important part of medical practice and that it will be one of the industries that this Nation has in the 21st century that will be leading edge, high-technology industry.

I can't give you the shape of it or give you any estimate at this point of how we would see it in a percent of the Nation's GDP. I think it's far too early to tell that. But I think it's clear that what we have here is the potential to offer individual help with very specific diseases, rather than sort of generic treatments over a larger group of individuals. In other words, to tailor the treatment to the individual.

Mr. VALENTINE. In your opinion, Dr. Greenwood, how can the government be of maximum assistance, except bailing money and sending it?

Dr. GREENWOOD. Well, I think the government can be of maximum assistance in two ways. One is if not bailing money into it at least continuing to understand that to support this type of research does cost money, especially in its early discovery stages.

I think we also have to think carefully about what creates the incentives in this country for investors to invest in the development of the associated technologies and industries. And those are probably the two most important things we can do. I guess the third thing I would say is careful regulation. A full understanding of what we are doing and its consequences.

Mr. VALENTINE. Could you give us the benefit of your thoughts regarding possible future use of gene therapy with reproductive cells?

Dr. GREENWOOD. I think we are a very long ways from being able to predict what the appropriate gene therapy usage would be in germ cell lines or reproductive cell lines. I have to be honest with—

you and say that anything that I would say would be so speculative that it would be of essentially no scientific value now. The prospects for germ cell manipulation are distant in the point of view of the science that is available right now.

Mr. VALENTINE. Dr. Wivel, in your judgment, when can we expect scientists to develop gene therapy in reproductive cells?

Dr. WIVEL. I think that Dr. Greenwood has stated very articulately precisely the problem that faces us. Just to say at the moment the somatic cell gene therapy we have discussed today really involves nothing but gene addition. That is a major feat in itself. But to even consider germ line gene therapy one would have to see a technology that is elevated far beyond anything we are doing today.

One would have to assure that genes added to those reproductive cells did not have any untoward effects. Simply adding genes would not be good enough. So, in essence, one might have to consider cutting out a defective gene, inserting a normal gene, and being sure that that insertion did not in any way adversely affect growth and development. We are a long, long, long way from being able to do that.

In the absence of that technical ability, germ line gene therapy has to be consigned to a fairly distant future.

Mr. VALENTINE. You mentioned the possibility of certain side effects.

Dr. WIVEL. Well, there are a number of good things that could happen when a gene is added to the genome. Conversely, there are a number of bad things that could happen. And let's just focus on two or three of the bad things that could happen. If a gene is inserted in the wrong place, it might have an adverse effect of shutting off another normal gene which was necessary to growth and development. If a gene is inserted in the wrong place, it might activate a proto-oncogene or a gene that predisposes to cancer, so that a proto-oncogene would become a oncogene. That would not be acceptable. Or a gene inserted in the wrong place might inactivate a tumor suppressor gene. Again, the result would be the tendency to develop cancer. All of those are untoward events which would not be tolerable indeed if one were contemplating gene therapy on reproductive cells.

Mr. VALENTINE. Thank you, Mr. Chairman.

We have some witnesses and I will yield back the balance of my time. I have questions to submit in writing. Thank you.

The CHAIRMAN. We will ask the witnesses to respond in writing to questions we don't have the opportunity to ask.

I am going to ask Mr. Valentine at this time to take over the Chair and encourage you to keep working on that gene to delay aging as much as possible. It will guarantee you more support from the Congress.

Mr. VALENTINE. [Presiding.] I had the benefit of that before I got here. I am really 32 years old. I have just been in Congress too long.

The Chair is happy to recognize Mrs. Morella.

Mrs. MORELLA. Thank you, Mr. Chairman.

I am delighted to be here and I am delighted with this topic. As you know, Mr. Chairman, I have the honor of representing the Na-

tional Institutes of Health, and I am just very proud of their achievements in so many areas and certainly what they have done with regard to gene therapy. And of course FDA is in my bailiwick, too, and I am very proud of the work together.

And I just hope that our consolidation is going to work out well, and I can assure you, Dr. Noguchi, I think it is right on track. And that will be great adding to our whole medical presence.

I also represent about 60 to 70 biotechnology companies right in Montgomery County, obviously there because of the proximity to NIH and to FDA. And I had just a couple of questions I will try to ask rather quickly because of the other two panels.

First of all, I remember a couple of years ago having the opportunity to be at a signing of a CRADA, which had Life Technologies from Gaithersburg and DOE and Livermore Lab, on mapping the human genome and that was kind of the beginning of it being on track in that kind of administrative or official way.

So I am very proud of what you are doing. I also took part in a Dana Farber genetic screening panel that came here to the Washington area and NIH had some involvement. This poses—I also spoke to a biotechnology group the other day—poses a number of other questions I would like to ask.

First of all, biotechnology, because of the risk-taking involved by companies, has a problem in terms of long-range gains because of the difficulty of knowing what they are going to find that is going to be helpful maybe to a small number.

And in Business Week—I think it was this week—Business Week has a cover story which is frightening. I don't believe it completely, but sometimes perception is so important in terms of how the biotechnology companies are perceived in terms of the future.

I guess I would ask you about that. How it fits into the problem of long-range commitment in terms of resources to come up with those discoveries. Plus, the fact that with the Dana Farber Forum, some of the concerns that came out is okay, so you find a gene, what have you discovered that someone as a propensity toward a disease and you tell that person that. Or do you not tell the person that because you don't have a cure for it?

And so you have got the trauma of, does this person then live knowing that I'm only going to live so many years or I'm going to have this happen to me. So there are a number of problems, I think, attached as we continue to develop and understand the genes and experiment and whatever.

So I guess I'm asking about your prognosis for the future, given the fact that there is always the downside in terms of the psychology of what you do with the discoveries genetically. And don't we have human genome in Rockville that has now up to 100,000 genes that they have discovered?

Any one of those comments that you would like to make. I am just very interested in the whole area and will continue with you either afterwards. Anything that you want to convey to me, it is a very important area to me.

Dr. WIVEL. Just in response to one of your comments, and I think you were perhaps touching on the issue of use of this technology for enhancement perhaps as opposed to treatment of disease or how differently it might be used. And clearly, that is an issue that

has come up for prolonged discussion and will continue to be a matter of discussion.

I think that all the polls of the public that have been taken thus far and information that is available, that there seems to be a general consensus that gene therapy is a very legitimate way to go in terms of treating disease. There is a consensus on that.

If one moves from that position to the element of using such technology for enhancement, then there may be grounds for disagreement. Perhaps one of those reasons is there is never going to be a consensus about what enhancement constitutes; what is important to one individual may be entirely unimportant to another. So part of the problem would derive that we would not have a consensus for using this technology for enhancement.

I think the position of the medical and scientific community would be that the techniques should be restricted to correction of disease processes and that alone.

Dr. NOGUCHI. I'd like to just address the biotechnology aspect, since that is one of the largest areas that we do regulate. I think if we go back to the beginning and through the history of biotechnology, part of the misconception that we have all made, I would posit, is that early on it was recognized that if there were diseases that we understood, such as diabetes, one could easily engineer a protein that could substitute for the porcine insulin and get good results.

The first biologic that was approved was Interferon. It was originally thought to be a magic bullet, but it was not a replacement therapy in that sense. That is, we did not know if anybody lacked Interferon and if there was a disease linked to that. And the only disease that was found was hairy cell leukemia, which has only 50 patients a year in America.

So part of the problem that we see is that there are diseases that are straightforward and there are diseases that are incredibly complex. Cancer comes to mind.

Obviously for biotechnology a very complex issue is sepsis. It does appear that the causes of sepsis are many and there are not one of simply replacing something.

I think one of the aspects of gene therapy therapy and the RAC process that has been fruitful is normally these kinds of knowledge of what works and doesn't is held by a few, very often not outside the company or the FDA. At least the initial RAC process, there are 70 to 80 trials ongoing, and a very public view of what is going on.

We do know what has some potential for working. We do know what doesn't really seem to be doing anything at the moment. So rather than painting a gloomy view of the picture, I would simply say that just as early vaccines showed us if you could prevent an infection specifically you could prevent a disease, just as biotechnology shows us you could cure a disease if you know what is missing, gene therapy is the same way.

And again, as we have stated, we see gene therapy as being only the tip of the iceberg. To do it, you need all the other biotechnology, including new devices as well. So I guess from the FDA's point of view, while we are officially neutral, we see the field as continuously and continually growing.

Mrs. MORELLA. Did you want to comment on that, Dr. Greenwood?

Dr. GREENWOOD. Well, you asked a series of fairly complex questions. The thing I guess I would like to say about the development of the biotechnology industry in the context of gene therapy, because gene therapy is only one of the many possibilities for development of what we now call the biotechnologies in this country, gene therapy may be quite a long ways away from significant commercialization of the therapy itself, although commercialization of delivery systems and things of that sort may certainly be possible in the nearer term.

The opportunities, though, for the biotechnology firms, many of whom I am familiar with in your district, are really probably in the more traditional medical area where the processes that can be used by biotechnology can be used to produce either a new product or to better produce a product that we know can and does work.

So to the extent that we are developing an environment where we can easily discover new ideas and then transfer them out into the commercial sector, I think that is a very important thing for us to continue doing in a partnership fashion with industry. I think that is probably an important point to leave in the record.

Mrs. MORELLA. Dr. Wivel, do you work with the biotechnology companies?

Dr. WIVEL. We do in an indirect way and some ways directly. We do in that the vast majority of the research proposals or protocols brought before the RAC represent a collaboration between academically based investigators and biotechnology companies. So there is a rather intense participation of those two groups represented in practically every protocol we see for review.

Mrs. MORELLA. Dr. Noguchi, I always hear that there is such a long delay with FDA, even though we have tried to help to speed the process. Are you making some significant strides in terms of the timeliness?

Dr. NOGUCHI. I can only really address the area of cell and gene therapy at this moment. I would say we're moving on the cell and gene therapy protocols. Again, these are not at any stage near the licensing or approval stage but in Phase I. We have a mandatory requirement that within 30 days of submission of the IND that we must approve it or not approve it. Typically that turns into a 21-day review by three professional people at the FDA, the product reviewer, a medical officer, and a toxicology reviewer. And then that often is discussed internally and sometimes externally if it happens to be an issue that we consider big enough in the RAC is simultaneously considering.

Very often during that time what we find is that the basic scientific principles are correct. However, the specifics, which is where FDA really gets very picky about it, is like when you are buying a house, you can go around and make a lot of different estimates but when it comes to handing over the mortgage, you really have to have the specifications in hand. When we ask for the final specifications on the product to be used in a human, we will wait until the tests are actually done and the results are in before the trial may go on.

So at least in the investigational stage, I think we are moving as rapidly as we can. Very often there are just simply technical problems on the company side. It takes time to do a test. It takes time to screen a culture, for example.

Mrs. MORELLA. I understand there have been problems of going beyond the 30 days but there is probably reason for it.

One final point, Dr. Wivel used the term enhancement. That is probably the correct term, but one of the points I was getting at is if you could isolate a gene that causes something, breast cancer, do you not have another psychological, ethical responsibility about whether you let a person know that they have that gene?

Dr. WIVEL. This is a commonly recurring problem and it does pose an ethical dilemma. And that is, do you inform people about a disease process with potentially serious effects, if at the same time you have absolutely nothing to offer in the way of treatment?

I could not make a general comment that could be interpreted as policy in this area, but I can say from the past, in history, in certain types of research protocols, that elements of that research were not allowed because in point of fact they would identify a potential problem and it was felt that it was not desirable to identify that and then have that patient have to cope with the anxiety of a possible untoward event.

I don't think there is any clear-cut answer to this, but it certainly is a dilemma, and it has been well emphasized by this recent discovery of the gene associated with different forms of breast cancer.

I think, as I say, in the past there have been times research protocols have been modified to prevent this dilemma from occurring.

Mrs. MORELLA. We know how the ramifications of this whole issue begin to expand, and at some other point I am sure we will hear from another panel for the need for money for further research and investment.

Thank you, Mr. Chairman. Thank you very much.

Mr. VALENTINE. The Chair is happy to recognize at this time the distinguished gentleman from Michigan, Dr. Ehlers. You see, we do have some superachievers in this body.

Doctor.

Dr. EHLERS. Some of them even grow beards. You are doing something I can't do.

Thank you, Mr. Chairman.

In the interest of time I will try to be brief. I just want to follow up on the very last sentence in your testimony, Dr. Noguchi, as relates to some questions asked earlier by Chairman Brown and Congresswoman Morella.

Everyone always complains, of course, about the regulatory aspects of the FDA and the slowness and so forth. But one particular complaint I have heard in this area of gene therapy is the difficulty of having to deal with both NIH and FDA, having to do different things for the two of them, and yet there is a lot of overlap.

Furthermore, having to totally redo documents for the FDA and NIH when just a small change is made in the process in gene therapy rather than being simply permitted to amend the protocols or the documents which have previously been submitted.

Your last comment, Dr. Noguchi, was that you were working with the NIH on improving the RAC process. What can you do to

streamline the regulatory process? It is bad enough to deal with one Federal agency, but dealing with two, it is not twice as bad. I think it goes as the square of the number of agencies involved.

And I am wondering if you are actively pursuing trying to improve that for the industry and the ability of simply offering amendments for changes in the ongoing research projects.

Dr. NOGUCHI. Those are very good points and useful comments, and yes, we actually can report on some progress and can tell you of some initiatives we have taken.

As one example, the idea of E-mail being used and electronic mail as well as the so-called Internet, information highway, is being used right now to revise the RAC guidelines in a very rapid and efficient manner just between staff and ourselves.

We recognize very much that if you look at the requirements of FDA and the requirements of the RAC process, that much of the forms and the questions that are asked are overlapping. They are somewhat divergent but they are overlapping.

FDA internally has a program that is being started to computerize the agency's ability to do things. And specifically, we have proposed and at least preliminarily we believe it will be a pilot project in which the database that is maintained by the RAC on the patients in this particular field, approximately 70, 75 protocols, a little over 200 patients, will be actually used as prototype for that. We would envision that the application process would be also an electronic type of form that it indeed could be amended as various requirements were added to it, rather than to redo the whole process.

I think in fact for us to be able to even envision and to comprehend the complexities if we don't have that online database and electronic submission, it will be simply impossible to do from the flood of papers. So I would say yes, we have some very strong commitments from FDA to the process.

Dr. EHLERS. Well, I appreciate that. And I think it is essential. But also I guess I would be a little concerned about assuming that computerization is going to solve it. I happen to be on Internet, too, and it is wonderful. But I think what is more important in the agency is a real sense of urgency that is real important. Even though it may not be extremely important to the agency, it is extremely important to the businesses dealing with it.

Many of them are on the economic fringe. We just heard a reference to the Business Week article, Congresswoman Morella referred to that. It is a tough field financially. And time is money to them.

And so I think it is fine, not only the computerization but generating a sense of urgency throughout both your agencies to deal with these things, rapidly recognizing the dollar signs that the companies have to deal with.

Dr. NOGUCHI. This particular initiative is in the commissioner's office and it has his backing and yes, we agree. It is not just the companies who are short on resources. Everyone is. So we totally agree with that.

Dr. EHLERS. Dr. Wivel?

Dr. WIVEL. I would like to make two comments on that. We already have in place two mechanisms for accelerating this process.

One is the so-called minor modifications capability, and that is protocols, once approved by the RAC, can have minor modifications without any requirement for major review again.

That process is handled entirely within our office. And those modifications go on continuously. The summary of those is given at the quarterly RAC meetings.

Second is that we have established a category for accelerated review. There are seven major parameters which determine whether or not a protocol qualifies for that. Accelerated review, again, means that full committee review is not at all required. And so we have protocols coming in now which are handled in that fashion. And we believe that both those mechanisms will speed up the process.

Dr. EHLERS. I am pleased to hear that.

Let me just—a final comment—make a suggestion. We, as Representatives of the people, always get invited to do things. Recently, I spent a half a day as a carpenter so I would understand the construction industry. And when I was in local government we would exchange with mayors and others for a day to see what other communities are like.

It might be worthwhile if you would trade places for a day with some of the researchers in the companies, not only for your benefit but also for theirs. I would like them to sit in your seat for a day. Obviously they can't view their competitors's proposals. But other than that, it might be useful to swap jobs for a day and get the perspective from the other side.

Thank you very much.

Mr. VALENTINE. The Chair thanks the gentleman, and Mr. Hoke has returned, but doesn't have any questions as I understand it.

We thank you very much for the preparations that went into your appearance here and coming and sharing these words of wisdom with us. It is possible that we may have some questions from other Members of the committee, some of whom have not been able to attend the meeting. And if you would answer those, we would appreciate it.

That brings us to panel two, which consists of Dr. Kenneth Culver, Iowa Methodist Medical Center in Des Moines, and the young patient who has been referred to, Ashanthi DeSilva and her father, Raj DeSilva of North Olmsted, Ohio.

Mr. HOKE. A fine suburb of Cleveland on the West Side.

Mr. VALENTINE. We have got that for the record.

Mr. HOKE. Thank you, Mr. Chairman.

Mr. VALENTINE. I understand this young lady has heard a lot of speeches today. I hear that she would rather be at school or the State fair or the ice rink. School, I am sure it was.

Dr. Culver, your statements—I don't know whether we received written statements from—we did? Well, your statements will appear in the record as presented, and we would appreciate it if you would summarize or otherwise proceed as you deem appropriate.

STATEMENTS OF DR. KENNETH CULVER, IOWA METHODIST MEDICAL CENTER, HUMAN GENE THERAPY RESEARCH INSTITUTE; AND ASHANTHI DESILVA, PATIENT, AND RAJ DESILVA

Dr. CULVER. Thank you, Mr. Chairman. It is a pleasure to be here to talk about a very special event, celebrating the fourth anniversary of the first gene therapy experiment that occurred at National Institutes of Health in September 1990.

As you will hear from the testimony from Raj and Ashanthi, and as you read in the documents, the DeSilvas are a very special family, not unlike many thousands of families around the United States who are dealing with particular types of genetic illnesses and disorders or handicaps and conditions that limit their ability to fully participate in their community.

It was recognized a long time ago that gene therapy is a new modality that can change that. Unlike any new technologies that have evolved in the last decades, gene therapy has the potential to change the isolated way many people live and to allow them to fully participate or substantially to a greater level[1] participate in life and productive life.

Much like the advent of antibiotics and immunizations and the way they changed the overall health of the world, gene therapy has that same potential. As we think about that, one has to recognize how we can as individuals in science or as legislators make certain that our public is aware of the potential, the risks as well as benefits, and how we can move forward in such a manner that as quickly and efficiently as possible, we can provide these novel new technologies to people in need.

I didn't realize the number of people who struggle with genetic illnesses until I was an intern in pediatrics at the University of California-San Francisco, and during those months and several years there I found that there were hundreds of kids under my care who suffered from genetic illnesses and cancer for which we had no curative therapy.

Sure, advances in modern medicine have given us wonderful new technologies that allowed us to treat the symptoms of disease; to stop seizures but not to solve the underlying neurologic problems; to be able to treat cancer but perhaps at great personal cost as well as health care cost; to be able to treat infections but not prevent the vulnerability to infections.

The bottom line is, we need curative therapies that treat all the manifestations of the disease, not simply the symptoms. We have all suffered through treatments for the common cold which oftentimes makes us drowsy and feel worse than if we had taken nothing at all. I believe over the next several decades we will see the new information in genetics change all of that and change medicine by giving us new tools.

It was through caring for kids in my residency program that I fell in love with kids with immune deficiency disorders. It was in 1972 when I was in high school that David, the Bubble Boy was born and lived for 13 years and died in 1984, 10 years ago, in that

[1]The witness wishes to delete everything after "level" and add "in life and to lead a productive life" to clarify sentence.

bubble, not of infectious disease. They did a wonderful job preventing[2] him from infection, but David died of cancer.

The whole idea is to be able to treat all the vulnerabilities of the disease and not just be limited to certain aspects.

Because of the struggle and seeing these kids suffer, and many of them dying in the bone marrow transplant unit, I left the University of California in 1987 and went to NIH to work with Drs. Michael Blaese and French Anderson to develop gene therapy for immune deficiency disorders.

We worked pretty much every day for three years trying to take the best that technology had to offer in the late 1980s as a way that we could apply to humans to treat adenosine deaminase deficiency. And it was on September 14th, 1990, about this time in the afternoon, that I injected a little over a billion cells into Ashanthi's hand that really, I think, had a significant impact on her health.

There were many hundreds of people who went before us, decades and decades ahead of us, who provided us the tools to make that day possible. But finally we realized the potential that is growing around us in almost every university and a in variety of companies around the United States to spread[3] to a whole variety of a great number of diseases.

As you will hear from Mr. DeSilva, Ashanthi has improved clinically, allowing her to remove herself from a life of isolation and go to public school. And you are right, sir, she would rather be in school than listening to us talk here today. And that is one of the greatest testimonies that we could have asked for.

We have treated a second child, Cynthia Cutshall, also from Ohio but from Canton, and she has also shown good clinical benefit as a result of this procedure, proving that the genetic alteration of defective cells can result in clear benefit to a human being.

We are struggling now to find ways to apply that[4] to people with a variety of immune deficiency disorders—cancer, autoimmune disorders, and HIV infection. I am confident that gene therapy is going to revolutionize the way we practice medicine. It isn't going to put surgeons out of business or any other subspecialty. It is going to change the tools that we have to use as physicians treat patients.

As result of that, there are going to be great financial benefits. And as I outlined in my written testimony, the current disorders that we are trying to treat—and "we" being the gene therapy group at large—trying to treat, such as cystic fibrosis, hemophilia, Gaucher's disease and ADA deficiency, has the potential that, if successful, would save $2 billion a year in health care funding.

And one of the things that I would suggest is that as Congress decides how to redistribute money in the way it pays for health care, that we can't forget that gene therapy may be our greatest savings in health care dollars as we move into the next 10 to 20 years.

And there are quite a large number of Ashanthi's in our country who are counting on us physicians and scientists and legislators to

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[2]The witness wishes to delete "preventing" and insert "protecting".
[3]Insert "these technologies" after "spread".
[4]Delete "that" and insert "gene therapy".

make a good-faith effort to make sure that everyone has their chance to get their treatment at the earliest possible time.

Thank you.

[The prepared statement of Dr. Culver follows:]

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GENE THERAPY: A BURGEONING REVOLUTION IN HEALTHCARE

U.S. House of Representatives Committee on
Science, Space and Technology

September 28, 1994

Introduction

Thank you. I am honored to be here to speak with the Committee today. My name is Kenneth W. Culver, M.D. I am a physician-scientist working at the Human Gene Therapy Research Institute in Des Moines, Iowa. The purpose of my presentation this afternoon is to highlight the significance of the 4th anniversary of the initiation of the first human gene therapy experiment and to illustrate its application and benefits through the case of Ashanthi V. DeSilva, the first person to benefit from the application of human gene therapy.[1]

For many decades, families, scientists and healthcare workers have hoped for genetic treatments. The hope was predicated on the belief that gene therapy would provide therapies for many of the 4000 known genetic disorders for which no suitable therapy now exists. Based upon a study published in 1983, only about 15% of genetic diseases have a therapy that allows them to lead a fully functional life.[2] Therefore, as this fourth anniversary of the first gene therapy experiment continues to show evidence of benefit without toxicity, enthusiasm for novel new genetic therapies continues to grow. We are becoming increasingly knowledgeable about the mechanisms by which genetics contribute to the development of acquired diseases such as cancer, autoimmune disease (e.g., rheumatoid arthritis, multiple sclerosis), heart disease and in susceptibility to infection. In addition to therapeutics, we have the potential to develop genetic vaccines to prevent infectious diseases, autoimmune disease and cancer. I have come to believe in the promise of gene therapy that was heralded by Dr. W. French Anderson and others since the 1970's because of personal struggles in caring for children with genetic diseases and cancer.[3]

Before speaking specifically about Ashanthi V. DeSilva and Cynthia M. Cutshall, our second patient, I would like to outline some of the fundamental beliefs about the young clinical discipline of human gene therapy.

Definition of Gene Therapy

> *"Gene therapy is the transfer of one or more genes into the tissues of a patient in an attempt to correct DNA abnormalities or alter DNA composition within targeted cells."*

This definition fundamentally means that gene therapy has the potential to prevent or treat essentially any human illness. Genes will be inserted to correct genetic deficiencies such as in the treatment of Cystic Fibrosis or Diabetes, to provide for the selective destruction of tumor cells or to immunize against infectious agents. As more human genes are mapped through the human genome project, the opportunities for gene therapy will expand. However, having knowledge of the gene map is not sufficient for therapeutic application. We also need to understand the function of the gene product and develop a method for delivery of the gene into the affected tissue. Therefore, simply isolating the gene can leave us years from a gene therapy application in humans.

Efficient gene delivery is currently the single greatest limitation to the broad application to human disease. This problem is highlighted by the fact that more than 4,000 human genes have now been isolated, but there are only seven gene therapy experiments for genetic diseases (table 1). At the Human Gene Therapy Research Institute, we are attempting to improve gene delivery by developing novel new methods for gene transfer. Fortunately, our pursuit for improved gene delivery is surrounded by a growing interest in academia and an

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1. Thompson, L. (1994): Correcting the Code. Simon & Shuster. New York.
2. Valle, D. (1987): Genetic Disease: An overview of current therapy. Hosp. Prac. July:167-182.
3. Anderson, W.F. (1984): Prospects for human gene therapy. Science. 226:401-409.

expanding biotechnology industry. Hopefully, the U.S. will remain the world leader in gene therapy, expediting the conversion of laboratory research in genetics into novel new therapies for patients worldwide. However, private, academic institutions such as ours, which are producing a substantial amount of the fundamental data on which new gene delivery methods are based are feeling the squeeze of the diminishing pool of medical research dollars. This will slow the speed of developing gene therapy into a clinical discipline and threaten the security of our world prominence in biotechnology and gene therapy.

Table 1: Approved Human Gene Therapy Experiments for Genetic Diseases

Genetic Disease	Tissue	Gene Transferred
Adenosine Deaminase Deficiency	T-cells & Marrow stem cells	ADA
Alpha-1-antitrypsin Deficiency	Respiratory Epithelium	α1AT
Cystic Fibrosis	Respiratory Epithelium	CF-TR
Familial Hypercholesterolemia	Hepatocytes	LDLr
Fanconi Anemia	Marrow stem cells	Compl. Group C
Gaucher Disease	Marrow stem cells	Glucocerebrosidase
Mucopolysaccharidosis type II	T-cells	Iduronate-2-sulfatase

Because gene therapy provides new opportunities for the treatment of human disease, I believe gene therapy will create a revolution in the practice of medicine and substantially alter the pharmaceutical industry. The ability to eliminate all manifestations of a certain disease through gene therapy instead of repeatedly treating the symptoms will save enormous costs for our entire healthcare system. More importantly, elimination of all symptoms of the disease will substantially reduce the amount of human suffering and improve the duration and productivity of the lives of the many thousands of our citizens.

Why I Became Involved in Gene Therapy Research

As a pediatric intern and resident at the University of California, San Francisco (UCSF), I became increasingly frustrated with the limits of medical technology. For many genetic diseases such as Cystic Fibrosis (CF) and acquired diseases (e.g., certain cancers), there is no curative or preventative genetic therapy. For instance, a number of therapies have contributed to an improvement in the life span of children with CF, but their lives usually continue to be complicated by expensive, chronic therapies. These symptomatic therapies diminish the number and severity of infections and treat the symptoms of the disease, but failed to treat the underlying genetic basis of the disorder. Likewise, certain forms of cancer therapy (e.g., chemotherapy, radiation) have been successful in prolonging life and curing some cancers, but the associated complications and side effects to normal tissues can add substantial suffering and expense to the cost of cancer therapy regardless of the outcome of the treatment. Gene therapy offers a new opportunity to selectively treat the fundamental basis of essentially all forms of human illness by eliminating all of the manifestations of the disease, perhaps even before the disease occurs. I came to appreciate the dream and promise of gene therapy through my caring for these desperate children and their families.

During my medical education, I developed an interest in immunity, the part of our bodies that protects us against infection, autoimmunity and malignancy. This led to my enrolling in a pediatric immunology fellowship program at UCSF after completing my pediatric residency. It was during my tenure in that program, that I cared for a large number of children and teenagers with life threatening genetic disorders and cancer. I grew increasingly frustrated because my patients usually died despite super human efforts by a very skilled healthcare team and the expenditure of tens of thousands of dollars because we had no treatment to

correct the genetic basis of their disease. There was one particular little girl, Chelsea Ward, whose living and dying gave my life a particular purpose, focusing my work toward the development of gene therapy for congenital severe combined immunodeficiency disorders (SCID). These disorders are commonly known as the "Bubble Boy Disease".[4] Chelsea had been one of my patients in the UCSF pediatric bone marrow transplant unit. She underwent two bone marrow transplants and died due to our inability to repair her immune system, leaving her unable to fight off bacterial, virus and fungal infections. Treating the symptoms of the infections with antibiotics and antiviral drugs ultimately failed.

With a determination to improve the quality of healthcare for children with immunodeficiency disorders, I moved to the National Institutes of Health (NIH) in July, 1987, to join the laboratory of Dr. R. Michael Blaese at the National Cancer Institute (NCI). He had been collaborating with Dr. W. French Anderson at the National Heart, Lung and Blood Institute (NHLBI) on the development of bone marrow gene therapy for ADA deficiency. Because the prospects for bone marrow gene therapy were poor, Dr. Blaese assigned me the task of developing T-lymphocyte gene therapy for a rare form of severe combined immunodeficiency, called Adenosine Deaminase (ADA) deficiency. T-lymphocytes are a type of white blood cell that protects us from cancer and infectious agents such as viruses and fungi. Children with SCID are deficient in functional T-lymphocytes and are very susceptible to overwhelming infection and cancer. I was very excited because this was the same genetic disorder that had led to Chelsea's immune system failure and her death.

Why ADA Deficiency Was The First Disorder Treated With Gene Therapy[5]

ADA deficiency was chosen as the first test of clinical gene therapy for the following reasons: (1) The gene was cloned in 1983 and subsequently, a large body of knowledge had accumulated about the gene and its function. ADA is considered a "housekeeping" gene because the gene is constantly producing the ADA enzyme for use in normal cellular metabolism. Screening studies of the general population have revealed that a 10% level ADA enzyme activity is found in some normal individuals and is consistent with normal immune functioning. This suggested that a 10% correction of the patients T-lymphocytes could potentially lead to substantial immunologic correction. Since we do not have gene delivery systems that are 100% efficient, this 10% feature is critical for attempting gene therapy at this stage of our technological development; (2) Normal individuals have been found with 50-fold the normal concentration of ADA enzyme in their cells. Therefore, if our insert gene would overexpress the ADA enzyme 50 times (an unlikely occurrence), we would not expect to harm our patients; (3) We determined that murine retroviral vectors (genetically-disabled mouse viruses) can efficiently and stably insert functional copies of the human ADA gene into cultured ADA deficient T-lymphocytes. Experiments with allogeneic bone marrow transplantation have determined that engraftment of T-lymphocytes alone can be curative and therefore, the genetic correction of T-lymphocytes may be beneficial. While bone marrow correction is our ultimate goal, because the marrow would continuously produce genetically-corrected T-lymphocytes, the regular infusion of genetically-corrected T-lymphocytes may therefore be an appropriate intermediate step until the technological problems with efficient bone marrow gene transfer have been overcome; (4) Insertion of a normal human ADA gene into ADA deficient T-lymphocytes restored normal biochemical functioning. In fact, genetically-corrected T-lymphocytes acquired the ability for normal growth in tissue culture compared to non-corrected duplicate cultures which grew poorly; and (5) the group of children to be enrolled in the study have not experienced complete immunologic reconstitution by any other form of therapy and are therefore at risk of opportunistic infection and malignancy.

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4. Culver, K.W. (1993): Splice of Life. Genetic therapy comes of age. The Sciences, 33:18-24.
5. Culver, K.W. (1994): Gene Therapy. A handbook for physicians. Mary Ann Liebert, New York,

Children afflicted with complete ADA deficiency do not produce normal antibody responses to immunization with standard childhood vaccines (e.g. tetanus, diphtheria). Skin testing reveals anergy (no response) to multiple antigens (e.g., tetanus, influenza). As a result, these children are unable to completely resolve viral infections such as common respiratory and gastrointestinal infections. For most of the children, one simple point mutations (a specific abnormality in one nucleotide out of the more than 30,000 in each copy of the gene) results in a failure of the immune system to protect against persistent viral and fungal infections, repeated bacterial infections and early onset malignancy.

Current Clinical treatments for ADA Deficiency

The treatment of choice for children with ADA deficiency is bone marrow transplantation when a sibling with an exact tissue type match is available as a donor. Matched sibling bone marrow transplants will cure most of the children (70-90%). Unfortunately, only about 20-30% of patients will have a matched sibling donor. Bone marrow transplantation with partially-matched (≥50%) marrow from parents, is less successful in ADA deficiency with only about 40% achieving successful engraftment.

For ADA deficient children, without an identically matched marrow donor, ADA enzyme replacement therapy is currently used. The use of ADA enzyme replacement therapy has been considered because the substrate (deoxyadenosine) that ADA normally metabolizes can freely diffuse across cell membranes. Without a normal ADA gene, deoxyadenosine accumulates in immune cells, the blood and tissues of the patient resulting in failure of the immune system. Systemic injection of an ADA enzyme functions as an osmotic gradient to remove and degrade the deoxyadenosine from the immune cells improving the ability of the immune system to function. Adagen® is the current form of enzyme replacement in clinical use. Adagen® is bovine (cow) ADA enzyme that has been conjugated to polyethylene glycol (PEG) to allow survival and function of the ADA enzyme in the body for days. Without the PEG, the ADA enzyme is degraded in minutes after injection. The weekly intramuscular injection of Adagen® has been generally helpful to many of the more than 30 children treated as evidenced by fewer infections and improved growth at a cost of $100,000-$200,000/patient/year. However, enzyme replacement does not provide full immune reconstitution and life expectancy is expected to be shortened without a curative treatment.

The Development of Gene Therapy for ADA Deficiency

Ideally, the genetic correction of ADA deficiency would involve insertion of a human ADA gene into bone marrow stem cells. The insertion of a normal ADA gene into marrow stem cells would theoretically correct the immunodeficiency resulting in normal immunity and a cure for a life time. Unfortunately, isolation of marrow stem cells has proven very difficult. In addition, the insertion of genes into marrow stem cells of monkeys and humans has been very inefficient (<1%). Recent advances in enrichment for marrow stem cells (separation from more mature, short-lived progenitor cells) and techniques to induce proliferation of the stem cell to allow more efficient gene transfer have made it possible to initiate the first attempts at stem cell genetic correction of ADA deficiency.[6,7] Thus, for ADA deficiency, the isolation of the gene has not been the primary obstacle to curative bone marrow gene therapy, but rather the development of an efficient gene delivery system.

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6. Bordignon, C., Mavilio, F., Ferrari, G., Servida, P., Ugazio, A.G., Notarangelo, L.D. and Gilboa, E. (1993): Transfer of the ADA gene into bone marrow cells and peripheral blood lymphocytes for the treatment of patients affected by ADA-deficient SCID. Human Gene Ther. 4:513-520.
7. Blaese, R.M., Culver, K.W., Anderson, W.F., Nienhuis, A., Dunbar, C., Chang, L., Mullen, C., Carter, C., and Leitman, S. (1993): Treatment of severe combined immunodeficiency disease (SCID) due to adenosine deaminase deficiency with CD34+ selected autologous peripheral blood cells transduced with a human ADA gene. Hum Gene Ther. 4:521-527.

Since the marrow stem cell could not be used for the gene therapy in 1990, we considered the possibility of genetically correcting the mature T-lymphocyte.[8] T-lymphocytes are very easy to grow from the blood and are much easier to genetically alter in the laboratory than marrow stem cells. The genetic correction of ADA deficient T-lymphocytes was thought to be potentially useful since transplantation of identical bone marrow will completely cure ADA deficiency if only the T-lymphocytes engraft. Engraftment of the other types of bone marrow cells (i.e. other types of white blood cells) is not necessary. Animal experiments proved that the insertion of vectors into mature T-lymphocytes did not harm the cells and that the genetically-altered T-lymphocytes could survive in vivo for months.[9] Experiments with ADA deficient human cells in the laboratory demonstrated that the insertion of a normal human ADA gene into an ADA deficient cell corrected the ADA abnormality and resulted in the production of normal amounts of functional ADA enzyme. In addition, the ADA gene-corrected T-lymphocytes grew like normal ADA-containing T-lymphocytes when compared to non-corrected ADA deficient T-lymphocytes. Together, these laboratory findings suggested that the periodic infusion of a genetically corrected T-lymphocytes might result in improved immune system functioning.

As a result, Drs. Blaese, Anderson and I pursued the development of a method for the genetic correction of T-lymphocytes for children with ADA Deficiency. In May, 1988, after extensive testing in the laboratory and in animals, I first received blood samples from Ashanthi and Cynthia and 3 other children who suffered from ADA deficiency. Ashi and Cindy were receiving medical care at the Rainbow Babies Children's Hospital in Cleveland, Ohio. The research conducted with their cells ultimately provided the final portion of the requisite data to allow the first application of human gene therapy.

The First Gene Therapy Trial[10]

One example of the potential of gene therapy as a new treatment modality is illustrated by the case of Ashanthi V. DeSilva. Ashanthi was born to her proud parents on September 2, 1986. Soon after the birth, her parents began to notice that Ashanthi was chronically ill with infections and grew poorly. As the parents took Ashanthi to one physician after another, they became increasingly concerned that she might have a severe, unusual immune system disorder. Unfortunately, that turned out to be the case. In 1988, the proper diagnosis was made, Ashanthi had ADA deficiency, a rare form of the "Bubble Boy Disease". She was treated with Adagen®. On Adagen® she had improved weight gain, a modest decrease in the number of infections and an improved quality of her life. However, despite receiving these weekly intramuscular injections of Adagen®, she still required isolation in her home and frequent treatments with antibiotics to minimize the number and severity of infections.

As our laboratory work with her white blood cells progressed at NIH, Dr. Blaese and I visited the DeSilva family in May, 1990, to discuss the possibility of her becoming the first recipient of human gene therapy. Our laboratory studies had found that her cells grew the easiest and that for despite nearly two years on Adagen® therapy, she still was without complete recovery of normal immune function. Therefore, she became the ideal candidate to be the first recipient of human gene therapy.

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8. Culver, K., Cornetta, K., Morgan, R., Morecki, S., Abersold, P., Kasid, A., Lotze, M., Rosenberg, S.A., Anderson, W.F., and Blaese, R.M. (1991): Lymphocytes as cellular vehicles for gene therapy in mouse and man. Proc Nat Acad Sci (USA) 88:3155-3159.
9. Culver, K.W., Morgan, R.A., Osborne, W.R.A., Lee, R.T., Lenschow, D. Able, C., Cornetta, K., Miller, A.D., Anderson, W.F., and Blaese, R.M.: In vivo expression and survival of gene-modified Rhesus T lymphocytes. Hum Gene Ther. 1:399-410, 1991.
10. Blaese, R.M., Culver, K.W. and Anderson W.F. (1990): The ADA human gene therapy clinical protocol. Human Gene Ther. 1:331-362.

On September 14, 1990, at 12:52 in the afternoon, I administered the first human gene therapy treatment to Ashanthi V. DeSilva in the Intensive Care Unit of the Warren Grant Magnuson Clinical Center on the NIH campus in Bethesda, Maryland. This was a great event for the family and Drs. Blaese, Anderson and myself, marking the end of a long road to gain the final approvals to initiate the trial. Ten days earlier we had removed T-lymphocytes from her blood stream. In order to correct the underlying genetic defect in her T-lymphocytes, we used a disabled mouse virus (retroviral vector) to transfer a normal copy of the human ADA gene into her T-lymphocytes. The FDA-certified retroviral vector was manufactured by Genetic Therapy Inc., a gene therapy biotechnology company in Gaithersburg, Maryland. Next, we grew the genetically-corrected cells to large numbers in tissue culture while we tested them for evidence of contamination by bacteria or fungus and confirmed proper functioning of the new ADA gene. Having passed all the safety testing, she received more than 1 billion cells over 45 minutes by a simple intravenous infusion.

Subsequent to that initial treatment on September 14, 1990, we have continued to infuse more genetically engineered T-lymphocytes every six to eight weeks for the next 10 months. During that time, there was a progressive increase in her T-lymphocytes numbers with an overall improvement in her health. Her number of infections decreased significantly despite her escape from homebound isolation. She enrolled in public school kindergarten in the fall of 1991. Since that time Ashanthi has completed public school kindergarten, first grade and second grade. She leads a life that is essentially no different from her classmates in third grade, with the exception that she still receives occasional administrations of genetically engineered cells and weekly injections of Adagen®. A second patient began receiving this therapy on January 31, 1991. This child, Cynthia M. Cutshall, a nine-year-old from Canton, Ohio, has also shown clinical improvement and an increase in T-lymphocytes in her blood stream. Both children have manifested clear evidence of improved immune function through a variety of laboratory tests.

We had attempted to enroll a third patient, but due to her worsening chronic lung disease, despite enzyme replacement therapy, she was clinically too unstable to undergo the treatment and died. Both Ashi and Cindy have received infusions of ADA gene-corrected cells over the past 4 year with no significant adverse effects. This protocol is now an outpatient procedure, allowing the children to return home several hours after the administration of the genetically-corrected T-lymphocytes. This highlights one of the promises of gene therapy....that this new therapeutic modality will not have significant toxicity requiring expensive inpatient treatment such as with bone marrow transplantation.

Both children developed normal numbers of T-lymphocytes in their blood.[11] This is important since one of the key aspects in mounting an effective immune response against invading microorganisms and preventing cancer is sufficient numbers of T-lymphocytes. Both children also developed clear evidence of improved immune function. The first laboratory evidence of improved immune function was the spontaneous production of antibodies called isohemagglutinins. Normal individuals spontaneously produce isohemagglutinins, which are antibodies to blood types different from their own. For example, a person with type A blood will spontaneously make antibodies to type B blood. Children with ADA deficiency do not make these antibodies. Following the initiation of infusion of autologous gene-corrected T-lymphocytes, both children have made normal quantities of the appropriate type of isohemagglutinin. This is a very important function, since the ability to make specific antibody is essential to the development of a protective immune response following infection or immunization.

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11. Culver, K.W. and Blaese, R.M. (1994): Gene therapy for adenosine deaminase deficiency and malignant solid tumors. In Gene Therapeutics, Wolff, J.A. (ed). Birkhauser, Boston, pgs. 256-273.

There has also been evidence of clinical improvement in each child.[12] Ashanthi had a dramatic decrease in her number of infections compared to her pre-gene therapy condition. This prompted the family to decrease their self-imposed homebound isolation, a common restriction used to help minimize the number of infections and enroll her in public school. She has occasionally been ill, but recovers in the same fashion as her siblings; a significantly different response compared to life before gene therapy. For Cynthia, she found relief from her chronic sinusitis and headaches as well as a decrease in the number of days she was ill compared to her condition with enzyme replacement alone.

This initial human gene therapy protocol has provided additional insights. First, the use of retroviral-mediated gene transfer has shown no evidence of adverse side effects resulting from 23 infusions of T-lymphocytes during the more than 4 years of observation in each of these 2 immunodeficient children. While a longer observation period is required, these vulnerable patients have tolerated the procedure well. Second, these findings suggest that there is an advantage to genetic correction as opposed to infusion of the missing gene product. Third, these findings set the stage for the genetic correction of T-lymphocytes in other disorders such as HIV infected patients.[13] And finally, this successful experiment has provided a foundation for the new era of genetic healing, demonstrating that gene transfer can provide benefit for patients.

What is Next for Gene Therapy For ADA Deficiency

The continuous immunologic improvement seen in Ashi and Cindy suggests that the genetic correction of T-lymphocytes can provide additional immunologic improvement beyond infusions of the missing protein. While the use of genetically-altered T-lymphocytes is not a one shot cure for ADA deficiency, it seems to provide continued improved overall health in combination with Adagen®. Once bone marrow stem cell gene therapy becomes a reality, we hope to be able to cure ADA deficient children with a single gene therapy treatment negating the need for enzyme replacement and repeated infusions of ADA gene-corrected T-lymphocytes.

Regulation of Gene Therapy

The United States is a leader in the development of safeguards for the application of human gene therapy. In 1976, federal guidelines for research involving recombinant DNA molecules were issued. These included both biological and physical containment standards and a regulatory process for oversight of recombinant DNA research by researchers supported directly or indirectly by funds from the National Institutes of Health (NIH). The guidelines require that covered institutions establish an institutional biosafety committee (IBC) to monitor the use of recombinant DNA in the laboratory, in micro-organisms, in animals and in humans. The office of recombinant DNA activities (ORDA) at NIH monitors the status of the local IBC committees and provides administrative functions for the Recombinant DNA Advisory Committee (RAC). The RAC is an advisory committee to the director of NIH that discusses each human gene therapy trial in a public forum.

There are a number of steps required for a proposed human clinical gene therapy trial to become fully approved. First, the protocol must be approved by the local IRB (institutional review board) and IBC. Reports from these committees are then forwarded to the RAC. Meeting at 3 month intervals, the RAC discusses in a open, public forum, the details of each

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12. Thompson, L. (1993): The first kids with new genes. Time. 141:50-53.
13. Walker, R., Blaese, R.M., Carter, C.S., Chang, L., Klein, H., Lane, H.C., Leitman, S.F., and Mullen, C.A. (1993): Clinical Protocol. A study of the safety and survival of the adoptive transfer of genetically marked syngeneic lymphocytes in HIV-infected identical twins. Human Gene Ther. 4:659-680.

protocol. RAC membership includes clinicians, scientists, attorneys, ethicists, theologians, housewives, business persons, etc. The diverse composition of the RAC is an attempt to involve as many perspectives as possible so that the best interests of patients, society and the investigators can be served. In addition to the RAC review process, each of the clinical trials must be approved by the FDA. Each of the vector delivery systems used in human gene transfer trials is considered a biologic and requires the filing of an investigation new drug (IND) application. Once the approval of the NIH director and the FDA has been approved, human experimentation can begin.

More than 200 individuals have received recombinant DNA in the U.S. Ongoing monitoring by the RAC has not identified significant, unexpected side effects related to gene transfer since experiments in humans began in 1989. I believe that this is in part related to the extensive national review process. Discussion regarding a streamlining of the review process is now underway. The efforts are aimed at tying the FDA and RAC reviews together to expedite the approval process, without losing the opportunities for public debate and participation. Currently, it takes a minimum of 6-12 months to achieve approvals from the various regulatory bodies for somatic cell gene therapy trials. Countries in Europe and Asia have developed or are in the process of developing review panels similar to the RAC in order to regulate the application of gene therapy to humans.

All gene therapy trials in the United States target somatic cells, the non-reproductive cells of the body. Therefore, we are making every effort to prevent the transfer of genes into reproductive tissues that could lead to alterations in our gene pool. Current gene therapy techniques are limited to somatic cells and we are using treatments that only affect individuals with life threatening diseases. As a result, the use of gene therapy at this stage of development has raised no significant ethical questions beyond those raised by bone marrow and organ transplantation. As the field advances and techniques are developed that might allow the consideration of germ line gene therapy (alteration of reproductive tissues), we as a society, will need to debate the appropriateness of the use of these new technologies.[14]

Advances in Gene Therapy Since September 14, 1990

Since September, 1990, when human gene therapy began, there has been a continuing significant increase in gene therapy clinical trials in the United States, Europe and in Asia. There are now more than 60 approved gene therapy trials in the United States. Despite these increases as depicted in figure 1, we are still very much in the infancy of the development of this critically important technology.

The United States is currently the undisputed global leader in the development of human gene therapy. The status quo for medical therapies will soon be history, replaced by a new era of genetic therapy. This new era will redefine the practice of medicine and the pharmaceutical industry on a worldwide level, just as immunizations and antibiotics did during the past century. Curing diseases with treatments developed and produced in the United States will save billions of dollars in healthcare and produce revenues through the worldwide sales of the treatments. To maintain this global leadership position, allowing the United States to derive the benefit of it labors, we need to bolster the infrastructure of the pharmaceutical and biotech industries, universities and private institutions, so that we can expedite the development and applications of novel new therapies to humans and protect our technologies from exploitation.

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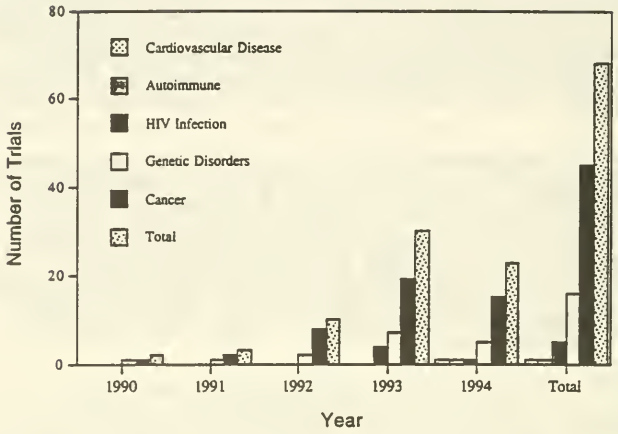
14. Wivel, N.A. and Walters, L (1993): Germ-line gene modification and disease prevention: Some medical and ethical perspectives. Science. 262:533-538.

Figure 1: Growth of RAC Approved Gene Therapy Trials In the United States



Gene Therapy for Cancer

Despite the multiple efforts toward the development of genetic therapies to cure genetic diseases, the most rapidly growing area of clinical gene therapy research is in the area of cancer (see figure 1). This has occurred in part because scientists must identify and characterize the function of each gene for each genetic disorder. However, in the case of cancer, a particular gene that destroys cancer cells may be useful in a variety of different cancers. This principle will likely hold true for autoimmune disorders (e.g., multiple sclerosis, rheumatoid arthritis) and infectious diseases.

Several years ago, I developed an idea about applying gene therapy to malignant brain tumors. Working with Dr. R. Michael Blaese and neurosurgeons Edward Oldfield and Zvi Ram at the National Institutes of Neurological Disorders and Stroke (NINDS), we created a gene transfer system that effectively destroyed brain tumors in rats without associated adverse side effects. The method uses the same general principles of recombinant DNA technology and gene transfer as in our ADA gene therapy trial. However, this technique does not insert a normal gene to restore genetic health, but rather inserts a new gene into an incurable cancer, to give the cancer a curable disease. This approach to brain tumors has demonstrated encouraging results and is now under investigation at 4 research centers in the United States.

Economic Benefits of Gene Therapy

There is no doubt that our emerging genetic technologies will revolutionize healthcare providing significant savings to the healthcare system. Focusing our energies on several genetic diseases that are either very expensive to treat or common, could save hundreds of millions of dollars in healthcare funds each year (see table 2).

Table 2: Estimated Yearly Cost to Care For Individuals with 4 Genetic Diseases*

Disease	Estimated Number Of Patients in the U.S.	Cost Per Patient Per Year	Total Cost Per Disease Per Year
ADA Deficiency	30	$100,000 - $200,000	$4,500,000
Cystic Fibrosis	30,000	$30,000 - $40,000	$1,050,000,000
Gaucher Disease (severe form receiving Ceredase®)	500	$150,000 - $250,000	$100,000,000
Hemophilia A & B (severe form)	13,000	$65,000	$845,000,000

* Statistics acquired from members of the Immune Deficiency Foundation, Cystic Fibrosis Foundation, the Hemophilia Foundation and the National Organization of Rare Disorders (NORD).

Gene therapy experiments in patients suffering from ADA deficiency, Cystic Fibrosis and Gaucher disease are in progress.[15] There is a significant effort to initiate gene therapy for hemophilia here in the United States. No experimental clinical trials have been proposed due to a lack of sufficient production of the missing clotting factor for a reasonable period of time in animal experiments. As depicted in Table 2, the total cost of care of individuals with these 4 disorders averages over $45,000 per year per patient, costing about $2 billion dollars per year. Even if gene therapy is relatively expensive, the ability to cure all the manifestations of the disease would obviously significantly outweigh the cost of therapy, with an enormous benefit to the patients and to the fiscal aspects of our healthcare system. It is extraordinary to consider that selectively targeting just a few genetic diseases where technological progress has been made could potentially cure these diseases in the next few years, resulting in personal, societal and financial benefits that would be astonishing.

Conclusion

We have witnessed the dawn of the era of genetic healing. In the first trial, we have demonstrated positive, long term health benefits as is evident in Ashanthi V. DeSilva. The process of transferring this new genetic information to other diseases is limited primarily by inadequate gene delivery systems. There is a growing number of private research centers, pharmaceutical companies and Biotechnology corporations who are preparing to expedite the development and application of gene therapy to humans. These prospects give us a very bright future for our own personal health as well as the economy of our country. Your support of this brave new form of healing will serve to make the dream a reality for the many who currently suffer from the lack of a satisfactory treatment for their desperate disease.

Thank you for your attention. I am willing to address questions from the committee members.

15. Beutler, E. (1992): Gaucher Disease: New molecular approaches to diagnosis and treatment. Science. 256:794-799.

Mr. VALENTINE. Thank you, sir.

Mr. DeSilva.

Mr. RAJ DESILVA. Thank you, Mr. Chairman. I wanted to try to get Ashanthi to say a few words to you, but she says she is bored.

Mr. VALENTINE. Well, they say honest confession is good for the soul.

Mr. RAJ DESILVA. My daughter, Ashanthi was born on September 2, 1986 in Colombo, Sri Lanka. She is the second of three girls. Her two sisters have suffered unrelated debilitating illness that has left them handicapped to differing degrees of motor dysfunction.

Ashanthi had a normal birth and was a reasonably healthy girl for about six months when she began to fall ill regularly and for extended periods with gradual weight loss. She was was under medication continuously and began to weaken to the point where she was unable to walk more than a few yards before she would need to stop and rest.

Vomiting and diarrhea were in her daily routine. The only nourishment she would accept was milk and a liquid food supplement. Of course, like most children, she would always accept a chocolate bar.

From the age of one year, my wife and I restricted her contact with children and people in general in the hope of reducing bouts of colds and influenza that she had become accustomed to. We prepared a so-called clean room for her at home. I washed my hands the moment I came home. Baby-sitters were out and staying home was in. My wife seldom left home for any reason. Visits to shopping malls were rare, as were visits to parks and restaurants. The family had become a hostage to our daughter's illness.

Fortuitously, the retesting of Ashanthi for allergies by Dr. Pascal in her office coincided with a telephone call from Ashanthi's pediatrician to Dr. Pascal. The pediatrician wished to know the meaning of laboratory results, for a basic immune response test requested by one of his patients. My wife immediately told Dr. Pascal of our request to this pediatrician to do an immune response test. Dr. Pascal verified that the laboratory test results were indeed for Ashanthi. She then made an appointment for Ashanthi to see Dr. Ricardo Sorenson of the University Hospitals of Cleveland, who worked for Dr. Melvin Berge, the head of the division of Immunology at the hospital. Dr. Berger previously worked at the National Institutes of Health.

Shortly after her second birthday on October 28, 1988, she was diagnosed as suffering from a rare condition known as severe combined immune deficiency, due to her body's inability to produce the enzyme adenosine deaminase, ADA. At that moment all we heard was that our little girl that we considered relatively the healthiest among our children, was in fact the one most in danger. As we learned later, this realization has a devastating effect on the parents of most children with immune system deficiencies.

Further, we had visited a total of nine pediatricians prior to this diagnosis, some many times. None of them had noticed that she had no detectable lymph or thymus glands, adenoids and tonsil, despite the numerous occasions that they had poked, prodded and X-rayed Ashanthi.

I believe it will be of interest to this committee that these nine pediatricians diagnosed Ashanthi to be suffering from milk allergy, roseola, bronchitis, asthma, upper respiratory and lower respiratory infections. One even suggested that her condition was due to brain damage.

Approval came quickly to place Ashanthi on the clinical trials for a new drug named PEG-ADA, developed by Enzon, a small biotech company. The treatment began on November 15, 1988. After an initial scare, when her platelet count dropped to very low levels, causing her to bruise when touched, she gradually began to gain weight and strength.

Despite her much improved condition, she continued a restricted lifestyle. She never did go to preschool and still had difficulty shaking off any illness that befell her.

It is my belief that PEG-ADA saved her life. I wish to give the Congress of the United States thanks for supporting the development of orphan drugs and treatments in the past. I encourage you to help expand this program.

Dr. Berge supplied Dr. Michael Blaese of NIH with samples of Ashanthi's blood. On September 14, 1990, shortly after her fourth birthday, she began gene therapy treatment. It was an attempt to replace her nonfunctional ADA gene with healthy genes in the hope that her immune system would begin to reconstitute.

Prior to the commencement of gene therapy experiment at NIH, Drs. Michael Blaese, French Anderson, Ken Cutler, and others at the NIH, went to extraordinary lengths to inform and educate my wife and me about gene therapy. Further, we discussed in great detail the potential benefits and risks involved, including the risks associated in venturing into the arena of human gene therapy.

Questions were answered without hesitation and in a straightforward manner. They were not afraid to say, We don't know. We discussed the gene therapy protocol for ADA, procedures for storage and handling of blood, equipment, testing labeling, duration, side effects, emergency and response both at the NIH and at home, and Ashanthi's tolerance for treatment and her comfort.

My wife and I will always remember and be grateful for the extraordinary effort and patience they displayed when answering our questions and addressing our concerns as we came back again and again for answers.

The gene therapy treatment itself was a nonevent from Ashanthi's point of view. No overnight hospital stay was required and the treatment no more painful than the PEG-ADA shot she received every week. A simple infusion of cells from a plastic bag hanging from a metal stand not unlike a blood transfusion lasting less than a hour constituted the treatment for that day.

Four to six months after the start of gene therapy, her energy level and general health had improved sufficiently for her to demand that she be allowed to go swimming and roller skating. Ashanthi has started her own road to emancipation and the freeing of her family from the self-imposed restrictive lifestyle.

A few months later, we proudly watched as she boarded a yellow school bus for the first time. Ashanthi received the last infusion of gene corrected cells in August 1992, over two years ago. During

this period, she continues to lead a normal life and is doing well in school.

Gene therapy has freed her from the shackles of ill-health. She now enjoys the freedom to play with friends and to go to school. Ashanthi considers herself fortunate to be able to have friends and hopes some day to become a physician and help others. Without gene therapy and the dedicated professionals who made it possible, Ashanthi would not be looking forward to a productive life.

But now, many of us are concerned that the next generation of scientists would not have the training needed to perform to the level of excellence that gave my daughter her new lease of life, due to the Federal budget cutbacks that have taken place, especially at the NIH.

Ashanthi's first infusion at the NIH took place on the 176th anniversary of Francis Scott Key composing the poem that became the National Anthem. The first gene therapy was another kind of "dawn's early light," one that gives hope to millions who suffer from hereditary disease, AIDS, and cancer.

Thank you.

[The prepared statement of Mr. DeSilva follows:]

COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY

September 28, 1994 HEARING

SUBJECT: GENE THERAPY

TESTIMONY: BY RAJ DE SILVA

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Ashanthi had a normal birth and was a reasonably healthy child for about six months, when she began to fall ill regularly and for extended periods with gradual weight loss. She was under medication continuously and began to weaken to the point where she as unable to walk more than a few yards before she would need to stop and rest. Vomiting and diarrhea were in her daily routine. The only nourishment she would accept was milk and a liquid food supplement. Of course, like most children she always would accept a chocolate bar. From the age of one year my wife and I restricted her contact with children and people in general, in the hope of reducing the bouts of colds and influenza that she had become accustomed to. We prepared a so called 'clean room' for her at home. I washed my hands the moment I came home. Baby sitters were out and staying home was in. My wife seldom left home for any reason. Visits to shopping malls were rare as were visits to parks and restaurants. The family had become a hostage to our daughter's illness.

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Shortly after her second birthday, on October 28, 1988, she was diagnosed as suffering from a rare condition known as severe combined immune deficiency (SCID), due to her body's inability to produce the enzyme adenosine deaminase (ADA). At that moment all we heard was that our little girl, that we considered relatively the healthiest among our children, was in fact the one most in danger. As we learned later this realization has a devastating effect on the parents of most children with immune system deficiencies. Further, we had visited a total of nine pediatricians prior to this diagnosis, some many times. None of them had noticed that she had no detectably lymph and thymus glands, adenoids and tonsils despite

the numerous occasions that they had poked, prodded and x-rayed Ashanthi. I believe it will be of interest to this committee that these nine pediatricians diagnosed Ashanthi to be suffering from milk allergy, roseola, bronchitis, asthma, upper respiratory and lower respiratory infections. One even suggested that her condition was due to brain damage.

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Ashanthi De Silva
Record of Medical Visits
Visits to:
Pediatrician
National
Institutes of Health
Number of Medical Visits
0
2
4
6
8
10
12
14
16
18
20
22
24
Year and Quarter
1986
1987
1988
1989
1990
1991
1992
1993
1994
4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4

Mr. VALENTINE. Thank you, sir. Thank both of you.

We have a vote, but I think we have time for a few more questions maybe.

Mr. DeSilva, this is, of course, very touching and very impressive presentation, and it is a very special time for all of us. You have other children?

Mr. RAJ DESILVA. I have two others.

Mr. VALENTINE. Two other children. Does your daughter—does this require continual treatment? Is she under medication now? Does she take medicine?

Mr. RAJ DESILVA. Ashanthi, the only medicine she takes is a continued PEG-ADA shot a weekly basis.

Mr. VALENTINE. What does this—except to the extent that you have mentioned in your prepared statement, I want to give you a chance to enlarge on this, what extent—what does this new technology mean to you and your family and how has it affected your quality of life?

Mr. RAJ DESILVA. When we suspected that Ashanthi was suffering from something other than what the doctors were telling us, we basically isolated ourselves. We were afraid that if we went out and came back a cold, that Ashanthi would get it because she had a terrible time shaking off any cold, normal influenza virus, and she was continuously on medication.

So basically what is meant was that my wife, basically, stayed home almost all day. She sometimes didn't go out anywhere for weeks. I did all the grocery shopping and I became very good at that. But—

Mr. VALENTINE. Good enough to continue?

Mr. RAJ DESILVA. But—

Mr. VALENTINE. Is your wife here with you? Some of us might want to cross-examine her to see if you were that great.

Mr. RAJ DESILVA. She would have liked to have been here but she is looking after the other girls at home. But what it meant was even for me, I had to, in my job, I had to—although I tried my best to do everything I was asked to do, sometimes I had to take some days off.

Mr. VALENTINE. What type of work are you in?

Mr. RAJ DESILVA. I am a project manager for B. F. Goodrich. I am a chemical engineer by profession. Although the company I worked for was very generous and very good about it, I didn't feel good about it. And our inability to have friends at home, to take our children out and let them play with other children, it is hard for me to think back or to describe how difficult life had become.

Thanks to Dr. Culver and the others at the NIH, we are freed from all of that now. And we are enjoying our life to the fullest.

Mr. VALENTINE. Was the health care plan that you had adequate? What can you tell us—I don't want to get into any of your private business, but it would be of some interest to us if you could tell us something about the cost of this.

Mr. RAJ DESILVA. The company I worked for gave me my health plan. And they wrote me a letter very generously saying not to worry about any of the costs. But in terms of the PEG-ADA treatment, the cost of the drug was very, very high. But since she had

been in a clinical trial, the company of Enzon that made the drug, agreed to defray the cost of the drug for her.

So in terms of having to pay for it, we didn't have to pay for the treatment. And the NIH treatment was basically taken up by the taxpayers. And I am very much obliged for that.

Mr. VALENTINE. Mr. Hoke, can you come back with us? I was going to say, you could question now, but I think we are down to about four or five minutes. We have got to go vote, so please hang with us. This will give the young lady a recess period.

[Recess.]

Mr. VALENTINE. Mr. DeSilva, I would like to leave an open invitation with the young lady to participate whenever she feels like it. If she has anything she would like to say on reflection or if she would like to come up here and make a speech.

Okay. Dr. Culver, you know you are talking to lay people, so I know that some of the questions that I am going to ask, you are going to say, Well, maybe that is self-evident. But how specifically is gene therapy novel and revolutionary?

Dr. CULVER. What differentiates gene therapy from most other therapies out there is the possibility of correcting all the manifestizations of a disease. When a child inherits the genetic defect for cystic fibrosis, they will have lung disease, and a variety of manifestations because all the cells in the body are deficient, but the most severe are in the lung.

If we could put a normal gene into the lung, then all of the problems in the lung should go away. If we could deliver a gene into the bowel, we would theoretically allow these kids to live a normal lifetime.

The same[5] for immune deficiency disorder. We could give gallons of antibiotics and antifungal drugs, but the infections will come back as soon as we finish giving the drug until we fix the immune system.

Gene therapy really is an opportunity that we can actually cure diseases like muscular dystrophy, cystic fibrosis and ADA deficiency so that the kids won't be encumbered by the processes accompanying those disorders.

Mr. VALENTINE. How can this therapy be advanced or what should be the role of the United States Congress?

Dr. CULVER. You know, I have got a number of ideas on how the United States Congress and the community could work together. First of all, the March of Dimes did a study several years ago and asked the question of a thousand adults, What are your feelings about gene therapy, and 89 percent said we think gene therapy is good.

And then they asked how many people knew what it was and the same percent said they didn't know. I think one of the obligations that we have is[6] that gene therapy is a revolution in medicine. Gene transfer is a revolution in agriculture and it is going to change dramatically the pharmaceutical industry and the practice of medicine and what we need is a public who is educated and who can interpret questions posed to them by their physician whether

[5]The witness wishes to insert the words "is true" after "same" to complete meaning of sentence.

[6]The witness wishes to insert "to recognize" after "is" to complete thought.

they want a genetic test or gene therapy and understand the consequences if they choose to have that or not have that. An education program that is broadly based is critical.

The second thing is that Congress then as a part of that has to understand the significance of it and I am pleased that I and others have an opportunity to speak about this today.

Thirdly, it takes money to make this a reality. And I think it is by the generosity of the United States population that Ashanthi was able to receive this, a very experimental therapy at one of the best institutions we could ever build.

To make it a reality for the more than 5,000 known genetic disorders and the acquired diseases like cancer and autoimmune diseases like rheumatoid arthritis and multiple sclerosis, as well as infectious diseases, it is going to take money.

Health care reform offers us an opportunity to take a look at the long-term impact of what choices Congress might make and I would hope that one of the things that would figure prominently is that guaranteed funding to make sure that these technologies are of a prime priority.

Because the money will come back and the U.S., who is the leader in the development of these technologies, will be able to market this technology at home and abroad to bring us the revenues and not allow this technology to move outside the U.S. as it has with other technologies developed here. So a healthy business environment would be another aspect.

And lastly, one of the things that makes the development of these genetic therapies so expensive is clinical trial funding. We are now conducting a gene therapy trial at my institution in Des Moines for the treatment of brain tumors. It cost about $40- or $50,000 a patient in the early stages of trying to develop this therapy. But to take it all the way through and develop a license is going to cost many, many millions of dollars, and ways in which additional funding can be made available to test these in patients so that we can learn as quickly as possible if they will work will help the entire field more forward.

Mr. VALENTINE. Can you describe for us specific research agendas which are now in place in your shop, and how your institute is currently funded?

Dr. CULVER. The Human Gene Therapy Research Institute is one of the first private institutes in the United States specifically dedicated to working on gene therapy. We are focusing on cancer with 30 staff members and our goal is to continue our brain tumor gene therapy trials as we move towards ovarian cancer and colon cancer.

But the single biggest problem in gene therapy today is gene delivery. So we have a whole variety of programs looking at novel new ways to get the genes into the diseased tissues of the body so that we can move forward in gene therapy.

It is important for the committee to recognize that the Human Genome Project is providing us with the genes required to treat these diseases. But if we don't have ways to deliver them, we will know all the genes, but we won't have ways to deliver them.

So what we're trying to do in our institute is develop novel ways so as more information is gathered in the Human Genome Project, that we can apply it to human disease.

It is an exciting time, and I think we will see many more of these private institutions that partner along with biotechnology and pharmaceutical companies so that together we can move forward as expeditiously as possible.

Mr. VALENTINE. The gentleman from Ohio, Mr. Hoke.

Mr. HOKE. Thank you, Mr. Chairman. Thank you for calling this hearing. I am particularly pleased that we have some people from North Olmsted with us.

I wanted to say a couple of things and then some questions.

Dr. Culver, I am excited to hear that you were trained at University of California at San Francisco. My middle child, my oldest son was born with a hemifacial microsomia, and there is a particularly highly regarded craniofacial group out there that we did a consult with and got extremely good advice. So I am a little bit familiar with the department. And I am sure you know, you probably did a round in that area. It is very impressive.

I wanted to point out, because—and I am sure, Mr. DeSilva, that you are speaking on information that has probably been given to you, but I think for the record it is important to point out what NIH has been doing in this area and what NIH's budget has been as well because you had stated that you were concerned that the next generation of scientists wouldn't have the training needed to perform as a result of Federal budget cutbacks that have taken place, especially at the NIH.

I really feel constrained to set forth the facts with respect to the budgets at the NIH. We had a 1994 appropriation of $10.938 billion, we have a 1995 conference agreement of $11.44 billion. That is a $400 million increase at NIH. And when it comes specifically to gene therapy, we spent in fiscal 1991, $58 million; in fiscal year 1992, 92 million; and fiscal 93, 132 million. The estimate for fiscal 1994 is 148 million and the estimate for fiscal 1995 is $163 million.

So, I point these things out because, as I say, I am sure that you were given this information by somebody that helped you prepare remarks and I just think it's important for the record to let you and the public know how much money this Congress, your Congress, the people's Congress, is committing to these things because it hasn't been cut back at all. In fact, it has been significantly increased.

Mr. RAJ DESILVA. Thank you very much, Mr. Hoke. I think, I must have phrased that wrong from what you are telling me. But maybe it is a problem within the NIH because from what I hear, the training grounds within the NIH, the trainers of the new scientists within the NIH, those funds are being cut back.

And having been to the NIH a number of times, I have learned that the training that they receive at the NIH, the scientists and doctors that receive training at the NIH, they are, they go out into the private sector, and that training holds them—it does well for them.

And I think it does well for everybody in the United States and in the world to have well-trained people, and that's basically what I was referring to.

Mr. HOKE. Well, I don't know that the details of that account, but—and I—so I'm so glad that you are here with Ashanti. And she has been helped in this way and I would—I do not, under any cir-

cumstances, want you to become a pawn in what—or a tool of anybody in what becomes sort of a funding battle.

And I would hate to think that anyone at any government agency would ever exploit an individual citizen for their own purposes in a funding battle, and that's really why I am bringing this up; in no way to point any fingers at you, just so we are clear on that.

Mr. RAJ DESILVA. Thank you, Mr. Hoke.

Mr. HOKE. I had a couple thoughts. Are you with the Aerospace Division at Goodrich?

Mr. RAJ DESILVA. No, I am in the Specialty Chemicals Business Division.

Mr. HOKE. Was John Long part of the—

Mr. RAJ DESILVA. He's CEO.

Mr. HOKE. Was he part of that decision to see to it that Ashanti was going to have medical care no matter what?

Mr. RAJ DESILVA. I really don't deal with that level.

Mr. HOKE. At any rate, I am glad to hear that Goodrich stepped up to the plate on that one. I think that's a great reflection of corporate responsibility.

You want to say something, Mr. Chairman?

Mr. VALENTINE. No, I thought better of it.

Mr. HOKE. Dr. Culver, how many children are born annually with SCID, approximately?

Dr. CULVER. It is roughly about 40 a year in North America of which about 10 will have ADA deficiency. It's quite a rare disorder.

Mr. HOKE. Do we—we have only treated Ashanti and one other child now, right?

Dr. CULVER. In the initial protocol where we are genetically altering the T-lymphocytes, the kind of white cells in the blood, there are just two. Other children have been treated by using umbilical blood when they were diagnosed prenatally and known[7] they had the disease and we could save the umbilical cord blood.

So now there are four or five kids in the United States with ADA deficiency who have received gene therapy and about another five in Europe, so there is about—

Mr. HOKE. Is it hard to identify the kids to be able to get them, because apparently this has been extremely and miraculously successful in Ashanti's case.

Dr. CULVER. It is clear there is no question that Ashanti has had significant improvement in her ability to live, especially outside of her isolation at home, because of the infusion of the gene therapy on top of the PEG-ADA. It is hard to diagnose. It is a rare disorder. It occurs in one in every 1,000[8] to 500,000 births, so it is not routinely screened for.

A simple blood test can tell you if ADA deficiency is there or if you are a carrier for the disorder. Normally we know ahead only if there has been one infected child and the parents choose to have prenatal testing done subsequently.

Mr. HOKE. Because absent—I mean, with that small of a market, absent this kind of government funded research and effort, there

[7]The witness wishes to insert "to have" after "known".
[8]The witness has replaced "1,000" for "100,000".

probably would never be enough people to be able to market justifiable—

Dr. CULVER. That's true of many of the known genetic disorders and it poses a problem as we go forward about making certain that people have the opportunity for this technology to benefit them, all people.

Mr. HOKE. Do we ever get to economies of scale in this kind of research? I mean as we know more about it.

Dr. CULVER. I don't know that I am qualified to answer that question. Certainly the Orphan Drug Act seems to have helped provide incentives to companies to work on these rare disorders and perhaps if there is a day in which the gene delivery vehicles are standard and it is a matter of switching in one gene for another, that it might be practical to do that on a limited basis.

But my expectation is for these really rare diseases, it is going to be the function of the National Institutes of Health or some specialized centers with independent funding that are going to be able to treat those individuals.

Mr. HOKE. Ashanti. Could I ask you a question? I am over here. He's in the middle, but it is hard to tell.

Mr. VALENTINE. Honey, he's that ugly guy over here.

Mr. HOKE. That's right.

What school are you at now?

Ms. ASHANTI DESILVA. Forest School.

Mr. HOKE. Forest School. What grade are you in?

Ms. ASHANTI DESILVA. Third.

Mr. HOKE. Third grade. When did you start going there?

Ms. ASHANTI DESILVA. Two years ago.

Mr. HOKE. Two years ago. And in first grade or second grade?

Ms. ASHANTI DESILVA. First grade.

Mr. HOKE. In first grade. Can you remember what it was like when you were able to be able to be going to school the first time and not being at home all the time? Was it better to be able to get out and meet the other kids?

Ms. ASHANTI DESILVA. Yeah.

Mr. HOKE. Well, we're really glad that the work at the NIH was able to help you. And we're very, very glad that you are able to be with us here today. I think it's a wonderful story that you bring and some day you'll appreciate why we are all so grateful that you are here. We don't expect you to appreciate that now at your age in the third grade, but some day you will recognize how special that is.

Those are the only questions that I have, Mr. Chairman.

Mr. VALENTINE. Thank you, sir. And I take back what I said about that.

The lady from Washington, Ms. Dunn, do you have questions?

Ms. DUNN. Thank you, Mr. Chairman. I have no questions but I certainly am glad that Dr. Culver and the DeSilvas are here with us today and particularly that Ashanti is here. I am glad to have heard a portion of the story from Chairman Brown on the Floor of the House so that I could get over and hear the tail end of this. Thanks for being here with us.

Thank you, Mr. Chairman.

Mr. VALENTINE. Thank you. Thank you very much.

I speak for all of us, Chairman Brown, and all Members of the committee and say to you that we appreciate your coming and sharing this time with us. And I want to say for myself and for Chairman Brown that you know there are so many things, the House has been in session since we have been seated here, and there are so many other things that demand attention of Members that you should not judge the lack of attendance here as any feeling adverse to your missions in an effort to help you address these problems.

We would ask you to respond within reason to questions that might come to you from Members of the committee, within a reasonable length of time and reasonable questions. With that, thank you very much and, my dear, school is out.

Next panel, number three, consists of Dr. Jeffrey Swarz, Vice President, CS First Boston Corporation; Mr. Robert Abbott, Chief Executive Officer, Viagene, Inc.; and Dr. LeRoy Walters, Kennedy Institute for Ethics, Georgetown University.

Dr. Swarz.

STATEMENTS OF JEFFREY SWARZ, VICE PRESIDENT, CS FIRST BOSTON CORPORATION; LeROY WALTERS, KENNEDY INSTITUTE FOR ETHICS, GEORGETOWN UNIVERSITY; AND ROBERT ABBOTT, CHIEF EXECUTIVE OFFICER, VIAGENE, INC.

Mr. SWARZ. Good afternoon. I'm a Vice President and biotechnology analyst for the investment bank of CS First Boston. My Ph.D. is in neuroscience and I have been a biotechnology analyst on Wall Street for the past eight years.

CS First Boston is part of the international Swiss bank Credit Suisse. Our firm is an investment bank which participates in the trading of stocks and bonds as well as the financing of both public and private corporations. CS First Boston has been an active participant in the financing of biotechnology companies over the[9] five years. We provide the financial expertise needed to raise capital in the equity markets and we execute the actual sale of a company's stock to investors.

I have been asked to convey to this committee my views on the financing of gene therapy companies. Wall Street's view of gene therapy and other medical advances have gone from enthusiasm to one of interested bystander. The myriad of new technologies and terminologies initially had Wall Street investors confused, some not knowing the difference between DNA and the NBA.

Over the past 10 years, Wall Street has become more medically sophisticated. However it is important to remember that one of Wall Street's main responsibilities is to create wealth for shareholders. It is not avarice, as some cynics might suggest. Part of Wall Street's job is to manage money including the pension money of Congress and the President.

The goal of money management is to create the largest shareholder returns with minimal risks. Often when this precept is ignored, hundreds of millions of dollars can be lost. An example would be derivative trading. Many biotechnology companies, in-

[9]The witness wishes to insert "past" after "the".

cluding gene therapy companies, have few products and no earnings and therefore are viewed as very risky investments.

Compounding the current biotechnology investment climate is the political nightmare called health care reform. The President as well as certain Members of Congress have been urging price controls and other drug price review boards to oversee the pricing of new drugs. Although it is now clear that there will be no health care reform this year, this type of proposal may be reintroduced next year. Price controls, if instituted, would be disastrous for the biotechnology industry.

In order to compensate for the inherent high level of risk, investors expect high returns on biotechnology investments. Any form of price controls would limit those returns. If returns are going to be limited, then the incentive to invest in these companies is greatly diminished.

Again, remember the goal of managing money is to maximize profit and minimize risk. Thus even the perception of increased risk will cause investors to avoid biotechnology companies. This risk aversion was manifest in the declining prices of biotechnology stocks during the first six months of 1994. This is coincident with the high rhetoric of price controls coming from Washington.

The American Stock Exchange Biotech Index fell 33 percent and the Chicago Board Options Exchange Biotech Index fell 28 percent in the first half of 1994. Dozens of biotechnology companies now face the prospect of bankruptcy within the next 12 to 24 months because they have not been able to raise capital in this environment.

Gene therapy companies have been no exception to the rule: Maximize profit, minimize risk. Although there are over a dozen publicly traded gene therapy companies, most have found it very difficult to raise capital in the current uncertain climate of the government health care reform. Likewise, because of the early stage of gene therapy research and the long lead time needed to develop and receive FDA approval for a drug, gene therapy companies are viewed as particularly risky investments. In fact, in the last six months, there has been very limited public financing of biotechnology companies.

Those companies that have found financing have done so mainly in the private markets at greatly discounted prices or through corporate partnerships. Thus it could not be emphasized strongly enough that the market's perception of government interference is cause for Wall Street to not invest in biotechnology companies.

To be sure, as gene therapy companies continue to have clinical success with their products, Wall Street will eventually take notice. However, if the political climate is inhospitable to these medical technologies, if political expediency is put ahead of long-term medical progress, if political demagogy continues to flourish in spite of economic facts, then gene therapy and future medical breakthroughs may be put at risk to the overall detriment of the Nation.

The financing of gene therapy companies by Wall Street investors is inextricably linked to the laws set down by Congress that promote or hinder the development of new technologies. If future health care reform includes price controls of any sort, then gene therapy and future new medical technologies may not be financed

in the U.S. and many companies may have to turn overseas to find funding.

I urge Members of this distinguished committee to follow the first law of medicine set down by the great physician Hippocrates: First do no harm. Allow current biotechnology and future gene therapy products to flourish in the marketplace without the specter of government inference. This should allow these companies to find a more hospitable environment on Wall Street.

What you do here in Congress has as much to do with the future success of gene therapy as the scientist in the lab or the investor in New York. Remember, we must not lose sight of what we have gained in the past in our rush to shape what we desire in the future.

Thank you.

[The prepared statement of Mr. Swarz follows:]

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Testimony of Jeffrey R. Swarz, Ph.D.

CS First Boston

Before the

Committee on Science, Space and

Technology

September 28, 1994

Testimony of Jeffrey R. Swarz, Ph.D.
CS First Boston
Before the
Committee on Science, Space and Technology
September 28, 1994

Good afternoon. My name is Dr. Jeffrey Robert Swarz. I am a vice-president and biotechnology analyst for the investment bank of CS First Boston. My Ph.D. is in Neuroscience and I have been a biotechnology analyst on Wall Street for the past eight years. CS First Boston is part of the international Swiss bank Credit Suisse. Our firm is an investment bank which participates in the trading of stocks and bonds as well as the financing of both public and private corporations. CS First Boston has been an active participant in the financing of biotechnology companies over the past five years. We provide the financial expertise needed to raise capital in the equity markets and we execute the actual sale of a company's stock to investors. Venture capitalists function differently than an investment bank in that the venture capital firm typically provides the "seed money" needed to start a company while an investment bank generally works with more mature companies.

I have been asked to convey to this committee my views on the financing of gene therapy companies. To understand the financial communities view of new medical technologies like gene therapy and Wall Street's perspective on financing these companies one must first step back and answer the question how does Wall Street view the advances in medical technology in today's current healthcare climate.

I strongly believe, to paraphrase the late Aldous Huxley, that medicine stands on the verge of a brave new world. The harnessing of the human genome is already opening vast new vistas of molecular exploration. Through the pioneering work in the early 1970's of Drs. Dan Nathan and Hamilton Smith at the Johns Hopkins Medical School and Drs. Stan Cohen and Herb Boyer at Stanford University and the University of California San Francisco scientist were able for the first time to manipulate and transfer pieces of DNA, the basic building block of all life, from one species of organism to another. That singular achievement signaled the beginning of a new dawn in medicine and drug development.

Ever since a small company in Germany named Bayer in the late nineteenth century discovered aspirin, organic chemistry has dominated the discovery and the development of new drugs. In the past 100 years the field of organic chemistry and the pharmaceutical firms that exploited organic chemistry have brought the world thousands of life saving drugs that have literally saved the lives of millions of people and at a small cost relative to no therapy or poor therapy.

However, the fundamental molecular discoveries made in the early 1970's signaled, I believe, the end of organic chemistry as the primary approach to the discovery of new

drugs and ushered in the age of genetic engineering, i.e. the manipulation of genes for the production of new products. Interestingly, most of the major pharmaceutical firms ignored these new genetic discoveries and by doing so allowed an entire new industry based on biotechnology to develop. Companies such as Amgen, Biogen, Genentech, Chiron and Genzyme have discovered products that could never have been made using organic chemistry. Further, these drugs have saved thousands of lives since their introduction into society beginning in the late 1980's and include Neupogen, Epogen, Activase, Protropin, Ceredase, Betaseron, Proleukin, Intron A, Roferon, Pulmozyme and the vaccine Engerix B. Over 250 public biotechnology companies now exist. They generate revenues of over $6 billion per year. The vast majority of these companies are less than 10 years old.

Furthermore, once scientists learned how to cut up or splice DNA and then clone pieces of DNA it was a logical step to attempt to decipher the entire human genome. And it is through the knowledge gained from this undertaking that medicine is on the verge of its next leap forward, gene therapy. The Human Genome Project is the culmination of 40 years of research into understanding the elegant molecule called DNA.

Accordingly, from my vantage point as an analyst, the paths pharmaceutical firms and biotechnology firms are taking towards the 21st century are clearly divergent. The major US pharmaceutical firms are in the process of buying distribution, i.e. patients. Perhaps, at the expense of new drug discovery. For it is clear that despite millions of R&D dollars having been spent over the last decade there are few new drugs coming out of the laboratories of the major pharmaceutical companies in the coming years.

This is not from lack of effort or commitment to research. It is, I believe, because the technology used to discover drugs changed and the traditional pharmaceutical firms were not able or were unwilling to embrace it in a timely fashion. As an example, the most innovative new drug to be used in the fight against cancer in the last decade, Neupogen, was developed by the biotechnology firm Amgen, not a pharmaceutical firm. Unfortunately, it would appear that these traditional pharmaceutical firms may miss a second technological revolution in medicine. The deciphering of the human gene is now leading to gene therapy.

Gene therapy is a reality today. Gene therapy or the insertion of a normal gene to replace or alter a dysfunctional or absent gene is underway in over eighty clinical trials worldwide. Already there have been marked successes in treating ADA disease, brain cancer, hypercholesterolemia, cystic fibrosis, and Duchenne's muscular dystrophy. There are over a dozen public gene therapy companies, and a score of private gene therapy companies today. These firms have the potential to generate billions of dollars in revenues over the next ten years and substantial profits for investors. As an example the treatment for primary brain cancer alone could generate $300 million per year in revenues. The majority of these firms have been formed in the last 3-4 years.

More importantly, gene therapy offers the hope of one day treating the cause of disease and not just its symptoms. Curing cystic fibrosis would be far more effective than treating its symptoms for 30 years. Gene therapy could also eliminate the need to inject highly toxic chemotherapeutic drugs into patients to treat cancer. Gene therapy would also be far more cost effective than any long term drug therapy now on the market. Ultimately, gene therapy could save the healthcare system many millions of

dollars. Finally, if gene therapy is the next technological advance in medicine, then it is vital for the US to maintain its leadership in this field in order to retain its worldwide leadership in medicine. Science does not stand still, sometimes in spite of the best efforts of governments. If the United States does not continue to advance in this field then other countries will.

Wall Streets view of these medical advances has gone from enthusiasm to one of interested bystander. The myriad of new technologies and terminologies initially had Wall Street investors confused, some not knowing the difference between DNA and the NBA. Over the past ten years Wall Street has become more medically sophisticated. However, it is important to remember that one of Wall Street's main responsibilities is to create wealth for shareholders. It is not avarice as some cynics might suggest. Part of Wall Street's job is to manage money (including the pension money of Congress and the President). The goal of money management is to create the largest shareholder returns with minimal risk. Often when this precept is ignored hundreds of millions of dollars can be lost e.g. derivative trading. Many biotechnology companies including gene therapy companies have few products and no earnings and, therefore, are viewed as very risky investments.

Compounding the current biotechnology investment climate is the political nightmare called healthcare reform. The President as well as certain members of Congress have been urging price controls and/or drug price review boards to oversee the pricing of new drugs. Although it is now widely believed that there will be no healthcare reform this year, this type of proposal may continue to be re-introduced. Price controls, if instituted, would be disastrous for the biotechnology industry. In order to compensate

for the inherent high level of risk investors expect high returns on biotechnology investments. Any form of price controls would limit those returns. This also includes the "reasonable pricing" clause as part of the NIH Technology Transfer Agreement. If returns are going to be limited, then the incentive to invest in these companies is greatly diminished. Again, remember the goal of managing money is to maximize profit and minimize risk. Thus, even the perception of increased risk will cause investors to eschew biotechnology companies. This risk aversion was manifest in the declining prices of biotechnology stocks during the first six months of 1994. The American Stock Exchange Biotech Index fell 33% and the Chicago Board Options Exchange fell 28% in the first half of 1994. Dozens of biotech companies now face the prospect of bankruptcy within the next 12-24 months because they cannot raise capital in this environment.

Gene Therapy companies have been no exception to the rule maximize profit, minimize risk. Although there are over a dozen publicly traded gene therapy companies most have found it very difficult to raise capital in the current uncertain climate of government healthcare reform. Likewise, because of the early stage of gene therapy research, and the long lead time needed to develop and receive FDA approval for a drug gene therapy companies are viewed as particularly risky investments. In fact in the last six months there has been very limited public financing of biotechnology companies. Those companies that have found financing have done so mainly in the private markets at greatly discounted prices or through corporate partnerships. **Thus, it cannot be emphasized strongly enough that the markets perception of government interference is cause for Wall Street to not invest in biotechnology companies.**

To be sure, as gene therapy companies continue to have clinical success with their products Wall Street will eventually take notice. However, if the political climate is inhospitable to these new medical technologies, if political expediency is put ahead of long term medical progress, if political demagogy continues to flourish in spite of economic facts, then gene therapy and future medical breakthroughs may be put at risk to the overall detriment of the nation.

The financing of gene therapy companies by Wall Street investors is inextricably linked to the laws set down by Congress that promote or hinder the development of new technologies. If future healthcare reform includes price controls of any sort then gene therapy and future new medical technologies may not be financed in the US and many companies may have to turn overseas to find funding.

I urge members of this distinguished committee to follow the first law of medicine set down by the great physician Hippocrates, first, do no harm. Allow biotechnology products to flourish in the marketplace without the specter of government interference. This should allow these companies to find a more hospitable environment on Wall Street. What you do here in Congress has as much to do with the future success of gene therapy as the scientist in the lab or the investor in New York.

Remember, we must not lose sight of what we have gained in the past, in our rush to shape what we desire in the future.

Thank You

TO: Greg Riddle

From: Jeff R. Swarz

Re: Requested Biography

September 8, 1994

Dr. Swarz is currently a Vice-President at CS First Boston, an investment bank, in New York. He has been on Wall Street for eight years as a securities analyst specializing in biotechnology stocks. Dr. Swarz holds a Ph.D. in Neuroscience from the University of Rochester and a B.S. (with Honors) in Biological Sciences from the University of California at Irvine. After receiving his Ph.D. in 1977 Dr. Swarz held a post-doctoral fellowship in Neurology at the Johns Hopkins School of Medicine. He also taught histology and cell biology at the medical school. While at Johns Hopkins Dr. Swarz was a science advisor (1975-1976) to the Senate Subcommittee on Science, Technology and Space then chaired by Senator Adlai Stevenson Jr. (D-Ill). After leaving Johns Hopkins he was a research associate at the National Institutes of Health (division of Virology). Dr. Swarz has published numerous scientific articles and has co-edited a book on Genetic Engineering. In 1986 he joined Goldman Sachs as a biotechnology analyst and in 1992 he left Goldman Sachs to join CS First Boston. He is married to the screenwriter Kathy H. Kafer.

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Mr. VALENTINE. Thank you, Doctor.

Dr. Walters.

Mr. WALTERS. Mr. Chairman and Members of the subcommittee, I appreciate the opportunity to discuss with you some of the ethical issues surrounding the new technology called human gene therapy.

My remarks will focus on three topics. First, ethical judgments about gene therapy; second, the current review process for gene therapy studies in the United States; and third, challenges for the future. In presenting each topic, I will put forward a thesis for discussion.

My first topic, then, is ethical judgments about gene therapy. Here my thesis is the following: There is an international consensus on the ethical acceptability of human gene therapy when it does not involve reproductive cells and when it is aimed at curing or preventing serious disease.

It is always difficult to identify the precise beginning of an ethical debate because all the participants in such a debate build on the ideas and arguments of their predecessors. But in the United States the modern debate about human gene therapy as an application of molecular biology goes back to at least the year 1967. In August of that year, Marshall Nirenberg of the National Heart Institute published a very interesting editorial in *Science* entitled, "Will Society Be Prepared?"

After reviewing recent advances in biochemical genetics, Nirenberg wrote, and I quote: "The point which deserves special emphasis is that man may be able to program his own cells with synthetic information long before he will be able to assess adequately the long-term consequences of such alterations, long before he will be able to formulate goals, and long before he can resolve the ethical and moral problems which will be raised.

"When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind. I state this problem well in advance of the need to resolve it because decisions concerning the application of this knowledge must ultimately be made by society and only an informed society, can make such decisions wisely."

A few months later, another eminent scientist, Joshua Lederberg of Stanford University, wrote a letter of response to the Nirenberg editorial. Lederberg's letter to *Science* was entitled, "Dangers of Reprogramming Cells." And part of his letter read as follows: "In an editorial, "Will Society Be Prepared?" Nirenberg wrote about the prospects of molecular genetics. No subject of policy is more important than this and it deserves the most critical debate.

"There is some danger that, whether so intended or not, Nirenberg's language could generate public misunderstandings that might undercut the very research needed to reach sufficient wisdom. His underlying concern, which I share, is that biological control might be used by a malevolent government to the peril of individual freedom."

A little later in the letter he wrote, "Our main concern must be to maximize the role of individual decision. This could be defeated by overenthusiastic policing of personal initiative and experimentation as well as by premature positive measures imposed by the state." The end of the letter from Lederberg.

Twenty-seven years have passed since Nirenberg and Lederberg exchanged their concerns about the science and ethics of genetically modifying human cells. At congressional hearings and academic symposia and in literally hundreds of articles and books, the ethical discussion has been carried forward around the world.

If we examine the record closely, we find that a remarkable international ethical consensus on the ethics of human gene therapy has emerged. This consensus is best reflected in a series of 28 policy statements published since 1979 by government committees and commissions, by professional groups, and by major religious organizations.

Without exception, the 28 policy statements find human gene therapy to be ethically acceptable if the technique involves only nonreproductive or somatic cells and if it is directed toward the cure or prevention of serious disease. This positive evaluation of somatic cell gene therapy has been made by government committees from many nations, including Australia, Canada, Denmark, France, Germany, the Netherlands, Sweden, the United Kingdom, and the United States.

The professional and religious groups sharing in this consensus are also highly diverse. They include the American Medical Association, the World Council of Churches, and Pope John Paul II speaking for the Roman Catholic religious community. On most issues in biomedical ethics, those three groups don't see exactly eye to eye.

I think the consensus that has been reached is that somatic cell gene therapy is simply an extension of current medical techniques, especially transplantation techniques, and is therefore not a qualitatively new step in ethical terms.

It should be noted that no similar ethical consensus exists on the issue of genetic changes that would be passed on to future generations. A substantial majority of the 28 policy statements disapprove of making inheritable genetic changes, either in principle or at the present time. Very few of these policy statements discuss the possibility of genetic enhancement. Those that do all reject this use of genetic technology.

My second topic is the review process for gene therapy in the United States. And here my central point is the following: The NIH Recombinant DNA Advisory Committee, which I will call The Advisory Committee, functions as a kind of national science and ethics advisory board for the field of human gene therapy.

Every three months, an interdisciplinary committee meets for two days in Bethesda to review eight to twelve new human gene therapy proposals. The 25-member committee is comprised of laboratory scientists, physicians, ethicists, lawyers and lay people. The committee holds all of its meetings in public and members of the press always attend the meetings and report on the proceedings.

At its most recent meeting on September 12th and 13th of this month, The Advisory Committee reviewed eight human gene therapy proposals. These proposals were focused on a variety of diseases. Four were focused on types of cancers. Two were directed toward cystic fibrosis. One was aimed at treating artery disease, bypassing blockages in blood vessels in arms and legs, and one was directed at a rare genetic disorder called Hunter's syndrome. There

is a missing enzyme and harmful products build up in the lungs, hearts and joints of patients with Hunter's syndrome and they usually die between the ages of 20 and 40.

The diverse membership of The Advisory Committee allows it to examine both scientific and ethical issues raised by the gene therapy proposals. An evolving set of research guidelines called the Points to Consider provides the basic framework for the committee's review. Within the points to consider, three questions emerge as central.

First, are the procedures outlined in the proposal likely to be safe for the research subjects who participate? Second, is the proposed research likely to be beneficial either to the subjects who participate or to the science of human gene therapy or to both? And third, will the people who are invited to participate in the study be properly informed about its primary goals and about the probable benefits, if any, and the risks of the study to them?

As far as I know, this advisory committee is a unique institution in the arena of science and health-related policy-making. It is a public interdisciplinary quasi-regulatory body that is attached to the principal U.S. funding agency for biomedical research, the National Institutes of Health.

The committee was established after a premature gene therapy attempt in 1980 but before any medical disasters had occurred. In fact, the committee began its work and developed the Points to Consider document before the scientific community was ready to present the first well-designed gene therapy proposal. In this sense, The Advisory Committee has been a proactive rather than a reactive body. It has accompanied the science and technology of gene therapy in the formative years of the field rather than attempting to recapture a genie that has already escaped.

But what of the future? In my view, the central challenge of the future is to maintain the openness and public accountability of research on human gene therapy. As we have heard from earlier panelists, the National Institutes of Health and the Food and Drug Administration are seeking to consolidate and streamline the review process for human gene therapy proposals.

If recent suggestions are implemented, all gene therapy proposals that closely resemble studies already approved by The Advisory Committee will be submitted only to the FDA. These very similar proposals will be reviewed internally by the FDA's very capable specialists on genetic and cellular therapies. However, proposals that are judged by the FDA and the NIH to include important novel elements will be reviewed in a public forum at quarterly advisory committee meetings.

How can this new process with one private track and one public track nonetheless remain accountable to the American people?

Here I can only express the views of one citizen and one member of The Advisory Committee. For at least the next few years in the development of gene therapy, both policymakers and private citizens will need ready access to two kinds of information.

First, a public register of all gene therapy studies being conducted or proposed, even if those studies are privately funded; and second, public follow-up reports on the number of human subjects

involved in gene therapy studies and on any adverse effects experienced by those subjects.

If these two kinds of information remain available under the new review system, both the general public and policymakers will be able to follow what is happening in the gene therapy field. These kinds of information will also reassure everyone that there will be no surprises, that no novel kinds of gene therapy studies will be carried on without prior public disclosure and the opportunity for public discussion.

Thank you very much.

[The prepared statement of Mr. Walters follows:]

STATEMENT ON ETHICS AND HUMAN GENE THERAPY
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
September 28, 1994

LeRoy Walters, Ph.D.
Professor of Philosophy and
Kennedy Professor of Christian Ethics
Kennedy Institute of Ethics
Georgetown University

Mr. Chairman and members of the Subcommittee: I appreciate the opportunity to discuss with you some of the ethical issues surrounding the new technology called human gene therapy.

1. There is an international consensus on the ethical acceptability of human gene therapy when it does not involve reproductive cells and when it is aimed at curing or preventing serious disease.

It is always difficult to mark the precise beginning of an ethical debate because all participants in such a debate build on the ideas and arguments of their predecessors. However, in the United States the modern debate about human gene therapy as an application of molecular biology goes back to at least 1967. In August of that year Marshall Nirenberg of the National Heart Institute published an editorial in Science entitled, "Will Society Be Prepared?" After reviewing recent advances in biochemical genetics, Nirenberg wrote:

> The point which deserves special emphasis is that man may be able to program his own cells with synthetic information long before he will be able to assess adequately the long-term consequences of such alterations, long before he will be able to formulate goals, and long before he can resolve the ethical and moral problems which will be raised. When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind. I state this problem well in advance of the need to resolve it, because decisions concerning the application of this knowledge must ultimately be made by society, and only an informed society can make such decisions wisely (Science 157 [11 August 1967], p. 633).

A few months later another eminent scientist, Joshua Lederberg of Stanford University, wrote a letter of response to the Nirenberg editorial. Lederberg's letter, entitled "Dangers of Reprogramming Cells," was published in the October 20th issue of Science. Excerpts follow.

> In an editorial, "Will society be prepared?" (11 Aug., p. 633), Nirenberg wrote about the prospects of molecular genetics . . .
>
> No subject of policy is more important than this, and it deserves the most critical debate. There is some danger that, whether so intended or not, Nirenberg's language could generate public misunderstandings that might undercut the very research needed to reach sufficient wisdom. His underlying concern, which I share is that biological control might be used by a malevolent government to the peril of individual freedom.
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> * * *
>
> Our main concern must be to maximize the role of individual decision. This could be defeated by overenthusiastic policing of personal initiative and experimentation as well as by premature positive measures imposed by the state (Science 158 [20 October 1967], p. 313).

Twenty-seven years have passed since Marshall Nirenberg and Joshua Lederberg exchanged their concerns about the science and ethics of genetically modifying human cells. At Congressional hearings and academic symposia and in literally hundreds of articles and books the ethical discussion has been carried forward around the world. If we examine the record closely, we find that a remarkable international ethical consensus on the ethics of human gene therapy has emerged. The consensus view adopts a moderate position, somewhere between the stances of Nirenberg and Lederberg. Like Nirenberg, the consensus view accepts the importance of assessing long-term consequences and the central role of an informed society. Like Lederberg, the consensus view affirms the importance of fostering research and recognizes the danger of excessive government regulation.

Since 1980 the international consensus on the ethics of human gene therapy has been reflected in a series of 28 policy statements by government committees and commissions, by professional groups, and by major religious organizations. Without exception, the 28 policy statements find human gene therapy to be ethically acceptable if the technique involves only non-reproductive (somatic) cells and if it is directed toward the cure or prevention of serious disease. This positive judgment of somatic-cell gene therapy is shared by highly diverse groups, including the American Medical Association, the World Council of Churches, and Pope John Paul II speaking for the Roman Catholic religious community. (Please see the list of policy statements included in the Appendix to this statement.) In other words, on the issue of somatic-cell gene therapy ethical commentators do not fall into polar positions labeled pro-choice and pro-life. Everyone adopts a position that respects the free choice of human subjects (or their parents) and of researchers, and everyone views human gene therapy as a potentially life-saving or life-extending intervention.

It should be noted that no similar ethical consensus exists on either the issue of genetic changes that would be passed on to future generations or the issue of genetic enhancement. A substantial majority of the policy statements disapprove of making inheritable genetic changes -- either in principle or at the present time. The few policy statements that discuss genetic enhancement all reject this use of genetic intervention techniques.

While the international ethical consensus supports the genetic modification of human cells in general, important practical questions remain. For example, which diseases are the best candidates for gene therapy? How much laboratory research should be done in the Petri dish and in animals before gene therapy is attempted in human beings? And how will the first human subjects be selected for this innovative kind of research? Some mechanism had to be found, or perhaps invented, to wrestle with these practical questions.

2. The NIH Recombinant DNA Advisory Committee (also called "the RAC") functions as a national science and ethics advisory board for the field of human gene therapy.

Every three months an interdisciplinary advisory committee meets for two days in Bethesda to review 8-12 new human gene therapy proposals. The 25-member committee is comprised of laboratory scientists, physicians, ethicists, lawyers, and laypeople. The committee holds all of its meetings in public, and members of the press always attend the meetings and report on the proceedings, sometimes in national newspapers, sometimes in the news sections of scientific journals, sometimes in more specialized publications. The recommendations of the RAC are forwarded to the Director of NIH. The committee's full name is the NIH Recombinant DNA Advisory Committee, or more concisely, "the RAC."

At its most recent meeting on September 12th and 13th of this month, the RAC reviewed eight human gene therapy proposals. These proposals were focused on the following diseases:

Various types of cancers: 4

Cystic fibrosis: 2

Hunter syndrome: 1

Artery disease (bypassing blockages in blood vessels): 1

The diverse membership of the RAC allows the committee to examine both scientific and ethical issues raised by the gene therapy proposals. An evolving set of research guidelines called the "Points to Consider" provides the basic framework for RAC review. Within the "Points to Consider" three questions emerge as central:

1. Are the procedures outlined in the proposal likely to be safe for the research subjects who participate?

2. Is the proposed research likely to be beneficial, either to the subjects who participate, or to the science of human gene therapy, or to both?

3. Will the people who are invited to participate in the study be properly informed about its primary goals and about the probable benefits (if any) and risks of the study to them?

Some questions raised by RAC members are primarily technical, for example, whether a vector that carries genes into target cells could become infectious. Other questions are both technical and ethical: Should children with a mild form of Hunter's syndrome be enrolled in the first phase of a gene therapy study, or should the innovative procedures of the study be tried first in adults? Still other questions are primarily ethical in character. For example, the initial versions of some consent forms do not clearly disclose that a study is designed only to look at whether a gene is successfully transferred into the subjects' cells, and is not intended to provide a therapeutic benefit to the subjects (who are also patients suffering from a serious disease).

So far as I know, the RAC is a unique institution in the arena of science and health-related policymaking. It is a public, interdisciplinary, quasi-regulatory body that is attached to the principal national funding agency for biomedical research. It was established after a premature gene-therapy attempt in 1980, but before any medical disasters had occurred. In fact, it began its work and developed the "Points to Consider" document before the scientific community was ready to present the first well-designed gene therapy proposal. In this sense, the RAC has been a proactive rather than a reactive body. It has accompanied the science and technology of gene therapy in the formative years of the field, rather than attempting to recapture a genie that had already escaped.

The Congress, the NIH, and a presidential advisory commission on bioethics all collaborated in the creation of this innovative review process. We would not have a RAC review process for gene therapy today if Mr. Albert Gore, Jr., then a House member from Tennessee, had not held hearings on "Human Genetic Engineering" in November of 1982. At that hearing Mr. Alexander Capron, Executive Director of the President's Commission on Bioethics, presented a report entitled Splicing Life, which suggested several oversight mechanisms for the emerging field of human gene therapy. However, these hearings and this report would have gathered dust on archival shelves if the National Institutes of Health and one of its existing advisory committees, the RAC, had not responded so creatively and vigorously. In early 1983 the RAC chair, Mr. Robert Mitchell, an attorney from Norwalk, California, asked his fellow RAC members to read the Splicing Life report and to consider accepting responsibility for reviewing gene therapy proposals on a case-by-case basis -- if and when such studies were ever put forward. To their credit the RAC members of that time accepted an expansion of their mandate, and the NIH Director, James Wyngaarden, supported their initiative.

3. The central challenge for the future is to maintain the openness and public accountability of research on human gene therapy.

Nudged by AIDS activists and biotechnology companies, the NIH and the FDA are seeking to consolidate and streamline the review process for human gene therapy proposals. This initiative has simply accelerated the RAC's own ongoing effort to simplify its review and to focus primary attention on proposals that raise novel scientific or ethical questions.

Under the proposed process for consolidated review, all gene therapy proposals that closely parallel studies already approved by the RAC will be submitted only to the FDA and will be reviewed internally by the FDA's very capable specialists on genetic and cellular therapies. Proposals that are judged by the FDA and NIH to include important novel elements will be reviewed in a public forum at quarterly RAC meetings.

How can this new process, with one private track and one public track, nonetheless remain accountable to the American people? Here I can only express the views of one citizen and one member of the RAC. For at least the next few years in the development of gene therapy, both policymakers and private citizens will need ready access two kinds of information: (1) a public register of all gene therapy studies being conducted or proposed, even if those studies are privately funded; and (2) follow-up reports on the number of human subjects involved in gene therapy studies and on any adverse effects experienced by those subjects.

The public register of proposed and ongoing gene therapy studies will keep everyone informed about the wide range of diseases and disorders that are being targeted by researchers. For each study this register should include the names of the researchers, their home institutions, the title of the study, the study plan (or protocol), the number of subjects to be enrolled, the consent form, a non-technical abstract, and the names of commercial sponsors or collaborators, if any. In addition to informing both private citizens and policymakers about the varied applications of gene therapy, the public register will reassure all interested persons that no qualitatively-new approaches to gene therapy are being undertaken without their knowledge.

Regular follow-up reports on approved gene therapy studies are a second aspect of public accountability for this new field. Prompt public disclosure of adverse effects will help to alert both researchers and candidate subjects to potential problems. In addition, the careful observer will be able to compare published reports on completed or ongoing studies with the total number of research subjects enrolled in all gene therapy studies. Thus, both the successes and the adverse effects of gene therapy will be able to be viewed within a larger context.

In summary, almost thirty years of discussion and debate have led to an international consensus on the ethics of human gene therapy. The consensus finds the use of gene therapy in non-reproductive cells to be ethically acceptable, when the therapy is directed against

serious diseases. In the United States the birth and infancy of gene therapy as a medical intervention have been accompanied by a unique public review process. The public review of both the science and ethics of gene therapy has been carried out by an interdisciplinary committee, the NIH RAC.

As we move to a new and more streamlined review process, the RAC will become advisory to both the NIH and the FDA on novel kinds of gene therapy. In this new system the review of some gene therapy proposals will be conducted in private rather in a public forum. However, the field of gene therapy will remain publicly accountable if all interested persons have ready access to two kinds of information: a public register of all gene therapy proposals and regular follow-up reports on the human subjects whose participation makes gene therapy research possible.

APPENDIX

POLICY STATEMENTS ON HUMAN GENE THERAPY: AN INTERNATIONAL CHRONOLOGY

1980

World Council of Churches, Conference on Faith, Science, and the Future, Faith and Science in an Unjust World

1982

Parliamentary Assembly, Council of Europe: Recommendation 934 (1982) on Genetic Engineering

World Council of Churches, Working Committee on Church and Society, Manipulating Life: Ethical Issues in Genetic Engineering

United States, President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research, Splicing Life report

1983

Pope John Paul II, Address on "The Ethics of Genetic Manipulation" to the 35th General Assembly of the World Medical Association in Venice

1984

Denmark, Indenrigsministeriet (Ministry of the Interior) Fremskridtets Pris (The Price of Progress)

Sweden, Gen-Ethikkommittén (Genetic Ethics Committee), Genetisk Integritet (Genetic Integrity)

U.S., Congress, Office of Technology Assessment, Human Gene Therapy: Background Paper

1985

U.S., National Institutes of Health, Human Gene Therapy Subcommittee (formerly, Working Group on Human Gene Therapy), "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols"

Federal Republic of Germany, Justice Minister and Minister for Research and Technology, Working Group (the Benda Commission), In-Vitro Fertilisation, Genomanalyse und Gentherapie (In Vitro Fertilization, Genome-Analysis, and Gene Therapy)

1986

National Council of Churches, Governing Board, policy statement on "Genetic Science for Human Benefit"

1987

German Federal Republic, Tenth Bundestag, Enquete-Kommission (Committee of Inquiry), Chancen und Risiken der Gentechnologie (Opportunities and Risks of Genetic Technology)

World Medical Association, "Statement on Genetic Counseling and Genetic Engineering" (39th World Medical Assembly, Madrid)

Canada, Medical Research Council, Guidelines on Research Involving Human Subjects

Australia, National Health and Medical Research Council, Medical Research Ethics Committee, Ethical Aspects of Research on Human Gene Therapy

1988

European Medical Research Councils, "Gene Therapy in Man"

American Medical Association, Council on Ethical and Judicial Affairs, "Opinion on Gene Therapy and Surrogate Mothers" [Report E: (I-88); title provided]

Switzerland, Commission d'Experts pour la Génétique Humaine et la Médecine de la Reproduction, Rapport (The Amstad-Report)

1989

Canada, Medical Research Council, Discussion Paper: Research on Gene Therapy in Humans: Background and Guidelines

European Commission, Working Party, Ethics of New Reproductive Technologies (The Glover Report)

World Council of Churches, Subunit on Church and Society, Biotechnology: Its Challenge to the Churches and the World

Netherlands, Dutch Health Council, Committee, Heredity: Science and Society: On the Possibilities and Limits of Genetic Testing and Gene Therapy

1990

Council for International Organizations of Medical Sciences (CIOMS), "Genetics, Ethics and Human Values: Human Genome Mapping, Genetic Screening and Gene Therapy (The Declaration of Inuyama)"

Canada, Medical Research Council, Guidelines for Research on Somatic Cell Gene Therapy in Humans

France, Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé, Avis sur la Thérapie Génique (Opinion on Gene Therapy)

1991

Norway, Ministry of Health and Social Affairs, Ethics Committee, Man and Biotechnology

1992

United Kingdom, Committee on the Ethics of Human Gene Therapy [the Clothier committee], Report

1993

Canada, Royal Commission on New Reproductive Technologies, "Gene Therapy and Genetic Alteration," Chapter 29 in Proceed with Care: Final Report

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Mr. VALENTINE. Thank you, sir.

Mr. Abbott.

Mr. ABBOTT. Thank you. Congressman Valentine, you are well known within our industry as a strong advocate of the industry and we very much appreciate your efforts over the last year during the health care reform debate.

I am not going to read my testimony in detail but rather just summarize some highlights and then would be happy to answer questions both on the technical as well as a business nature since my underlying background is both science and business.

Gene transfer, or gene therapy as it is more commonly referred to, actually can involve the delivery of either a human gene or a nonhuman gene into patients, and some of the gene therapy trials that are going on now actually involve the use of nonhuman genes being delivered into humans.

This may seem somewhat bizarre but, in fact, such types of gene therapy have been going on in this country under commercially approved products for about 30 years because live attenuated vaccines are in fact nothing more than gene transfer products, where you deliver a living virus, such as attenuated polio virus, to a patient or subject, that virus then enters the cell or cells of that patient, reproduces, making viral proteins and stimulating an immune response. And so, in effect, gene therapy has been in the stream of commerce for some time.

Our company has focused on gene therapy applications that are very similar to this process that I have just described—live attenuated vaccines—because we feel that this particular type of application of gene therapy, in contrast to many genetic diseases, can result in a much sooner commercialization.

The first product that we have been working on is in effect a gene therapy product to treat HIV where we take a retroviral vector, such as the type that has been used by Ken Culver, and we insert into it two of the genes from the HIV virus. The HIV virus has about a dozen genes, so only having two there doesn't permit the recreation of an HIV virus.

We then deliver this product to patients where the product enters their cells and produces just these two proteins of the HIV virus, but because they are made inside of the patient's cells rather than being injected into the circulation or into the muscle, these result in an immune response that is referred to as a killer T cell response or cytotoxic T cell response, versus the antibody type response that you would get with a recombinant protein vaccine.

It is now widely believed that this type of immune response is going to be an important key to treating HIV. All of the early vaccines that were developed which have provided disappointment over the last few years have been recombinant proteins and they generate very high antibody levels to HIV but they fail to adequately stimulate adequate killer T cell responses.

Perhaps not very common knowledge at this point is that the clinical trials with this particular product have advanced quite far and in fact we have treated in four different phase one safety studies on the order of about 50 or 60 patients and are preparing to launch in just a few months what will be the first multi-center

phase two clinical trial of gene therapy in the world, right here in the United States.

So the potential for commercialization of gene therapy, should this product work, is actually a lot closer to the present than I think most people appreciate or think of when they look at gene therapy. If efficacy should be shown in this product over the next year, then we would anticipate going into a pivotal study sometime toward the end of 1995.

Along with that, of course, being commercially motivated, we have had to construct a manufacturing facility. Our company already has two manufacturing facilities in San Diego where we reside. This is our third facility. It is our first one that has been built on a commercial scale and was finished in fact two weeks ago.

The facility is currently undergoing validation to comply with the Good Manufacturing Practices Guidelines and we expect that facility to be in operation producing material for the pivotal trial by next summer. The facility, if our dosing expectations are correct about the product, should be able to produce about a half a million patient doses per year.

So once again I think that the commercial path of gene therapy may be a lot further advanced than some people anticipate, although it is in an area that scientifically probably represents a base hit rather than a home run since, in effect, what we have done is taken live attenuated vaccine technology and created the recombinant equivalent of it which is a lot safer than live attenuated vaccines.

Also, I would like to comment, since GNPs are foremost in our minds right now, that despite the fact that there is a common belief that the FDA represents a serious impediment to the expedient development of drugs, the division that we interact with—which happens to be Dr. Noguchi's division—has been very flexible and cooperative. They have been quite responsive to our needs and, to my knowledge, to the needs of all of the gene therapy companies and do not in any way fit the mold that I often hear characterized by pharmaceutical companies, even some in the biotech industry and certainly by the occasional Member of Congress. So we don't find anything broken at least with the division that we interact with.

Our company, as a result of being a little bit further advanced in manufacturing processes, has attracted the attention of a lot of pharmaceutical companies and in fact we have three major pharmaceutical partners. One is Japanese, one is German, and one is U.S. We also have active discussions going on with seven other pharmaceutical companies to enter into additional programs for gene therapy. Surprisingly, however, all seven of these companies were European pharmaceutical companies.

And I think you will find in my written testimony the theme of concern over the fact that foreign pharmaceutical concerns are a lot more active in terms of the attention they are giving to gene therapy.

Even though pharmaceuticals are an international business, the American pharmaceutical industry has really been significantly distracted over the last year in terms of its ability to think long term about research strategy and, as a result, there is a very sig-

nificant and real buying opportunity in terms of foreign investors buying U.S. gene therapy capabilities that is going on. It has been going on for several years and if the current climate in the United States continues, at least as far as financing is concerned, then I expect that to continue.

Of course, as a U.S.-based company, and since practically all of our employees are Americans, we certainly have a sense of obligation to this country. However, our obligation we feel is foremost to the lives and health and elimination of suffering of American citizens and secondarily to economic considerations.

We have received as much or more financing overseas for our company than domestically and we have raised about $100 million, and certainly our priority would be to continue to seek that funding wherever it exists so that we can move forward the technology that the country needs for its health benefits.

Just in closing, I would say that that particular concern, that is the financial chill that the industry is now experiencing, represents the number one impediment to the commercialization of gene therapy. The number two impediment in my view is FDA-related but is not an FDA performance issue, it is an FDA resource issue.

And I believe that it is very important for user fees and other fees that have been implemented with the stated purpose of providing the FDA the resources that they need should be kept earmarked for those purposes because I believe that a lot of the delays that people see at the FDA are resource constraints and not motivational issues as might have been suggested earlier today.

And then the third area which represents potential impediment to gene therapy is the length of time and the uncertainty associated with the patenting process in the country. The Patent Office also appears to be severely resource constrained. Viagene filed its underlying patent applications back in 1988 and we have yet to have an issued patent in the United States. We are now waiting six years for the first patent to be issued and, in the meantime, even though those patents cover a lot of technology, that technology is being used by other gene therapy companies. And should we receive the patent claims that we believe we are entitled to, that is going to lead us into a position of conflict and a position of embarrassment, frankly, in terms of enforcing those in the face of some very meaningful and encouraging progress by other companies.

In closing, thank you very much for the opportunity to testify here today and I hope that this committee will continue to exert the legislative leadership that it has in the past with regard to the biotech industry.

[The prepared statement of Mr. Abbott follows:]

VIAGENE, INC.

TESTIMONY OF ROBERT T. ABBOTT PRESIDENT AND C.E.O. OF VIAGENE, INC. ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION BEFORE THE COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY

SEPTEMBER 28, 1994

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TESTIMONY OF ROBERT T. ABBOTT
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SEPTEMBER 28, 1994

Good afternoon. Let me first introduce myself. My name is Robert T. Abbott. I am the President and CEO of Viagene, the country's largest gene therapy company. My entire working career, 25 years, has been spent in health care, and includes academic, hospital and industry experience. Educationally, I trained in biochemistry and genetics as an undergraduate, and thereafter earned a Ph.D. in Pathology. Both degrees were earned in Canada at McGill University during the tumultuous period when Canada imposed socialized health care on its citizens. After returning to the United States to pursue my working career, I earned an MBA from the University of Missouri in St. Louis and attended Indiana University School of Law in Indianapolis for two years before committing to the time consuming challenges of scientific entrepreneurism. During nine years with the Dow Chemical Company, I played a significant role in establishing medical laboratories in New York, San Francisco, and St. Louis. These laboratories specialized in highly sophisticated tests to detect and monitor cancer and drugs of both therapy and abuse. Thereafter, I assisted in the establishment of Oncogen, an early biotechnology company located in Seattle. Oncogen is now owned by Bristol-Myers-Squibb Company. Next, I founded and led for six years as President and CEO, a biotech company called NeoRx, located in Seattle. NeoRx is a public biotechnology company pursuing pharmaceutical applications of monoclonal antibodies. It hopes to receive approval of its first product within the next year, a full 10 years and $100 million after founding. From NeoRx, I was recruited to San Diego to take over the leadership of Viagene at the beginning of 1991.

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VIAGENE'S GENE THERAPY RESEARCH

In 1991, Viagene was a financially fragile, 4 year old company of about 40 employees. Today, it is arguably the most financially stable of the gene therapy companies, and employs over 160 persons, including about 40 Ph.D.s or M.D.s. Annually, we spend approximately $25 million in gene therapy research and development. The company is focused primarily on developing treatments for serious viral infections (such as HIV) and cancers, although we do have a smaller effort in cardiovascular and genetic diseases. This is in contrast to the gene therapy sector in general, which tends to focus on genetic diseases and cancer.

On the surface this difference in focus may appear subtle. To the contrary, I believe it is profound, as well as indicative of two distinctly different types of biotechnology companies. Viagene's focus on viral diseases and cancers is merely a reflection of its commercial or product focus. Companies with a product focus will generally seek out those applications of a technology that have the least uncertainty with regard to efficacy. That is, the base hits. This strategy benefits our country by pushing forward the commercial horizons of a new science. These early product successes may sometimes be less dramatic scientifically, but they are sure-footed and long lasting in terms of impact.

The other strategy used by companies is the academic approach. This is characterized by dramatic scientific advances into new medical areas, such as new disease applications. Like academic science, this strategy is driven by the desire to be the first to enter an area of research. Historically, these achievements, and the preparations that led up to them, have occurred primarily in academic centers or at the National Institutes of Health. This is due to the often high level of technical complexity that surrounds the first application of a new scientific concept. Today, however, it is not uncommon for academicians to make preparations for dramatic scientific breakthroughs through the auspices of a venture capital-backed company. In effect, they have persuaded the private sector, sometimes including public investors, to invest in basic research, which traditionally has been the responsibility of universities and governments. Although some might argue that this could mislead investors, who may not appreciate the lack of product potential embodied in many of these procedures, it does benefit the country as a whole by pushing forward the academic horizons of science faster than could occur if government alone funded such basic science initiatives.

Viagene, by selecting the product focused approach to company growth, has had to concentrate on building expertise in later-stage, or applied, technology; specifically, in manufacturing processes, quality control procedures, and commercial clinical trial design and management. As a result, our company is now a world leader in these areas of gene therapy, particularly as they relate to the use of retroviral vectors, the workhorse method used by the gene transfer industry.

Of particular interest to the committee should be our company's plans to commence Phase II clinical studies of our HIV Immunotherapeutic later this year. This will be the first ever Phase II study of a gene therapy product on a multicenter, commercial scale. If this study should demonstrate significant product efficacy, it will place the HIV Immunotherapeutic on a much shorter approval timeline than the often quoted turn of the century time frame that many have projected for the world's first gene therapy product. Indeed, Viagene is prepared for such an outcome, having recently completed construction of our third manufacturing facility, a commercial-scale facility that we believe will be capable of producing up to one-half million patient doses per year of the HIV Immunotherapeutic. This facility is currently undergoing validation to bring it into compliance with the FDA's good manufacturing practices guidelines and we expect it to be in full operation by next summer.

VIAGENE'S TECHNOLOGY & PRODUCT FOCUS

Viagene uses retroviral vectors in most of its current gene therapy products, including our most advanced product, the HIV Immunotherapeutic. We use these vectors because they are efficient, cost-effective to produce, well understood, and have an unblemished safety profile in human clinical use. Industry-wide, over 200 patients have been treated with retroviral vectors and we are not aware of a single product related adverse event that has been reported.

Recently, the company has developed a new vector system based upon the Sindbis virus. Sindbis is a relatively non-infectious virus with limited disease causing potential for humans. This vector system appears to be a major development in gene transfer technology in that it can produce hundreds, perhaps thousands, of times more therapeutic protein than other known methods of gene transfer; and, without producing the high level

of unwanted viral proteins that lead to either neutralizing or allergic immune responses seen in vector systems based upon viruses such as adenovirus.

Viagene's initial product focus is the development of immunotherapeutic products that function by "mimicking" disease processes, thereby triggering potent immune responses to intracellular diseases such as persistent viral infections and cancers. These diseases often exist because the body has failed to mount an effective response to a foreign or altered protein.

Activating Cytotoxic T-Cells (Killer T-Cells)

Immunotherapeutics under development at Viagene are designed to overcome elements of the disease process that allow viruses and cancers to evade detection by the immune system. Viagene's immunotherapeutic drugs work by delivering genes that code for the production of specific foreign or altered proteins. These genes then express the foreign antigens in a manner that mimics infection and optimizes immune recognition and response.

Viagene uses genetically engineered viral vectors to deliver gene sequences into cells. This results in the intracellular production of specific proteins, which in turn activates a cytotoxic T-lymphocyte immune response. By contrast, if such proteins would be delivered as recombinant proteins or killed-virus type vaccines, they would instead need to be engulfed into the cells of the immune system for processing, which would result in stimulation primarily of an antibody response rather than a cytotoxic T-cell response. Cytotoxic T-cell responses are now believed to be the critical immune response that fights viral infections and possibly cancer, also.

HIV Immunotherapeutic

Viagene's lead product is an immunotherapeutic for the treatment of human immunodeficiency virus (HIV) infection, the virus associated with AIDS. The product employs a genetically engineered murine retroviral vector to achieve intracellular delivery of a gene sequence that codes for certain HIV proteins. The resulting intracellular production of these foreign proteins leads to a vigorous response of cytotoxic T-lymphocytes against cells infected with HIV.

The efficiency of this product in producing a CTL response has been demonstrated in a mouse model and in rhesus monkeys, and has now advanced into human clinical trials, where statistically significant cytotoxic T-cell responses have also been shown in patients infected with HIV. Of particular significance is the discovery in laboratory experiments that these CTL responses recognize the various strains or mutations of HIV. Thus, a CTL response that is elicited using a vector product derived from one strain of HIV can recognize and kill cells infected by most, if not all, other strains of HIV. This discovery has been confirmed using human cells infected with live HIV as targets.

To date, Viagene has only reported results on the four patients participating in our first clinical study. The goal of this study was to evaluate the safety of this gene therapy approach for treating HIV infection. Happily, there were no product-related adverse events during this study. During the study, which followed patients for 18 months during and after treatment, all four patients maintained or modestly increased their CD4 cell count. Although purely an anecdotal observation, the blood of one patient, which consistently tested positive for the presence of HIV before and during treatment, has tested below the limits of assay detection for HIV during the past 6 months. It is impossible to determine whether this is a consequence of the treatment because this initial study contained only four patients and was designed to demonstrate safety, not to determine efficacy. Nevertheless, with so many disappointments worldwide over the years in searching for a treatment for HIV infection, even anecdotal observations provide us with the encouragement we need to maintain our intensive efforts to successfully apply gene therapy in the treatment of this disease.

Other Immunotherapeutic Products

The gene transfer technology that Viagene has developed for its HIV immunotherapeutic products also holds great promise for the treatment of other serious viral infections, as well as certain cancers. Viagene's strategy is to apply this gene transfer technology to the treatment of other serious diseases, such as those caused by hepatitis B virus, herpes simplex virus, human papillomavirus and Epstein-Barr virus. The human papilloma and Epstein-Barr viruses are believed to be the causative agents leading to the development of cervical cancer and nasopharyngeal (nose and throat) cancer, respectively. Parasitic infections such as malaria and leprosy are also potential targets for Viagene's therapeutic approach.

Viagene's technology may also prove valuable in veterinary medicine. There is a great need for effective therapeutic products to treat diseases such as feline immunodeficiency virus (the equivalent of AIDS in cats), equine infectious anemia (a disease of horses), avian flu (a disease of chickens), and visna virus (which affects sheep).

Future Gene Transfer Products

Longer-term, other exciting applications of gene transfer technology also will be realized. Through the use of murine retroviral vectors and other gene transfer systems, it will be possible to deliver human gene sequences for the purpose of augmenting or replacing defective human genes that cause disease. First among these possibilities will be diseases whose gene products do not require targeting to a specific cell type or location in the body - for example, treatment of hemophilia A through the use of the gene sequence for Factor VIII protein. Later, effective treatments for diseases such as diabetes, cystic fibrosis, muscular dystrophy, certain types of emphysema, and certain diseases involving elevated blood cholesterol levels may also be achievable.

In summary, the field of gene transfer technology is opening the door to treatment opportunities that were only dreams just a decade ago.

Viagene's commercial, versus academic, focus has attracted a high level of attention from major pharmaceutical companies. Indeed, we believe our company's three corporate alliances exceed, in aggregate, the sum of corporate commitment in the rest of the gene therapy sector. During the past few years, we have received over $55 million in support from our partners and anticipate a comparable level during the next few years. Significantly, about 70% of this support has come from foreign partners, and when that portion is combined with the portion of our company's Initial Public Offering that was purchased by foreign investors, we have received about $43 million of support from foreign sources, equaling all funding which we have received domestically.

To summarize my comments about Viagene, our Company's future appears bright, and I feel that we have been blessed. Nevertheless, like many other biotechnology companies, we are not limited by technology, but by capital. As will undoubtedly be shown repeatedly by academic investigators over the next few years, gene therapy is a powerful technology. The key to a company's, or a country's, successful use of this

technology will be to use it responsibly and practically. Viagene and other gene therapy companies are each faced with dozens of existing product applications to pursue; hundreds or thousands if you believe in the practicality of the Human Genome Project. However, with expenditures in excess of $100 million dollars required to develop each new product, a small company can only expect to raise enough capital for a few products during the next ten year time frame. Thus, although Viagene is one of the more fortunate biotech companies in that we have substantial corporate partner commitments and cash reserves adequate for up to three years of operation, we, also, will need to raise substantial additional capital before we have approval of our first product.

CAPITAL SQUEEZE

As requested, I would now like to make some comments about the biotechnology industry in general, where the financial picture is not as rosy as it is at Viagene. Most second and third tier biotech companies have less than 18 months of funding, many have less than 12 months, and dozens have funding for less than six months. According to a recent report by Dr. Robert Goldberg of the Gordon Public Policy Center at Brandeis University, fully 75 percent of biotechnology companies have 2 or less years of capital left. Ernst & Young reports that biotech companies are raising capital now at 25 percent of their burn rate (the rate at which capital is being expended.) As has already been mentioned, there are approximately 1,300 U.S. biotechnology companies. That means that a staggering 975 companies will need to go to the market in the next two years or face going out of business, merging or selling rights to a larger firm.

The seriousness of this situation cannot be overstated. The financing climate for biotech companies is, frankly, hostile. Public offerings are essentially impossible to undertake because of the depressed value of most companies' stock. This effect is indiscriminate. Virtually all companies are affected, regardless of company performance.

For example, despite the optimistic picture I painted for you regarding Viagene, the total value of our company, according to our recent stock price, is about $40 million dollars. Since our company has $33 million in cash and several more millions of dollars worth of assets, this means that the total value being attributed to our products, our patents, and seven years of experience with our technology is only about $5 million. $5 million for products and technology that have taken over $50 million and 7 years to develop and that are still attracting investment from foreign pharmaceutical companies.

One of our foreign corporate partners summed this situation up perfectly last month: "$5 million? I'll take it!" And they will, if present conditions continue in the U.S.

Foreign acquisition of the U. S. Biotech industry is not the only potential consequence of the current harsh financing climate. The industry is now beginning to see significant layoffs. While the total number of jobs involved is insignificant to the nation's economy, I believe these layoffs will forever impact our industry because of the psychological damage that is occurring. Entrepreneurial companies are staffed heavily by people in the early, energetic part of their careers because of the long working hours and dedication required. Salaried employees often work 60 to 70 hours per week without additional compensation. They are motivated to do this because they share in the company's vision and identify with the entrepreneurial spirit of the workplace. When, and if, such a company has its first lay-off, an irreparable break in trust occurs between the company and its employees. Sadly, it is usually the survivors of the lay-off who are the most affected. From that point forward, the work ethic is never the same. I believe that the lay-offs that are now occurring, because of this longest-ever hostile financing environment, will forever change the productivity of our biotech industry, dulling it from what it has been previously.

As to the causes and remedies of the current financing climate, I merely join others in speculation. The issues are multi-faceted, so a single remedy likely will not cure the patient. The simplistic diagnosis is that there are too many companies chasing too little capital. Even without the current contraction in available capital, the ever increasing flow of venture capital-spurred companies, each with an ever increasing appetite for capital, had to eventually come into balance with the market's appetite.

Nevertheless, the current squeeze in available capital, now over two years old, has been extreme. Viagene performed its Initial Public Offering during this period. In addition to numerous breakfast, luncheon, and dinner presentations, we conducted 44 one-on-one meetings with potential institutional investors; our lead investment banker had only had one biotech client exceed that number of presentations. Consequently, I feel relatively well-informed about what has been on the minds of these investors recently.

It should come as no surprise to you that the debate over health care reform, and price controls in particular, has been a major issue. This debate, more than most legislative matters, seems to have been directed at the American people, rather than about

the American people. The publicity-seeking and confrontational manner in which some in the Congress and the Administration have conducted this debate has unnerved investors. The consequences of this have been harsher on the biotech industry than on the pharmaceutical industry. Unlike the pharmaceutical giants that some legislators and administration officials apparently believe must be reigned-in, biotech companies cannot go into financing hibernation for several years while living off of a suet-pot of product sales. Most biotech companies do not have any sales yet! As a result, we have been caught in the crossfire in this battle among giants. At this point in time, I believe that the damage inflicted on the biotechnology sector is so severe that a cessation in the battle over health care reform and price controls will not in and of itself be sufficient to lead our industry into a recovery. It is my view that proactivity on the part of Congress in the form of financing stimuli, such as tax incentives, will be necessary.

Nevertheless, within the biotech community, I believe that gene therapy companies will fare better than others. For sure, the gene therapy sector is suffering also. However, interest in gene therapy is high among pharmaceutical companies. Consequently, gene therapy companies will be better able to form strategic alliances than many sectors of the biotech industry. This interest may also suggest a greater likelihood for acquisition of gene therapy companies; consequently, I expect the flood of new gene therapy companies that have formed recently to continue, but at a slower pace. This is because a critical contributing factor in the start-up of venture capital funded companies is the opportunity for future liquidity for those early investors. Pharmaceutical company acquisition provides an alternative liquidity path to the traditional route of a public offering.

My only concern regarding pharmaceutical acquisition interest in gene therapy is that it is primarily non-domestic at this time. Domestic pharmaceutical companies have been so beaten-up during the health care debate, and so distracted by the resulting industry reorganization, that they seem less able to focus on long term research priorities. These companies are pre-occupied by shorter-term distribution issues. European and Japanese pharmaceutical companies are not under the same level of pressure. As a result, domination over the U.S. gene therapy industry is shaping up to be a one-two punch, first from Europe, then Japan. These companies appear to be more long-range in their strategic planning and have identified gene therapy as an important future component of medical and pharmaceutical practice.

THE REGULATORY CLIMATE

Finally, I have been asked to comment on certain policy issues that impact the development of gene therapy. I would like to make brief statements on a few ethical issues surrounding gene transfer, on government regulation of clinical trials and drug approval, on price controls, and on technology transfer.

As the capabilities of gene transfer technology expand, there will no doubt be numerous ethical issues that arise and will have to be dealt with. Based upon where the field is today, I see two particular issues that deserve public discussion sooner, rather than later. First, is the issue of germline transfer of genes. Although most people see this as an issue that concerns purposeful modification of human germ cells (ova or sperm), I believe the more important issue is inadvertent germline transfer. This will become more apparent in the near future as technology is developed to target gene therapy within the body. To the extent that such technology will involve intravenous administration of gene therapy products, there is a risk of the blood-born product reaching the ovaries or testes. This could result in inadvertent modification of germline tissue while trying to treat primary disease.

The second ethical issue involves the extent to which technically feasible, but commercially impractical, treatments will be rationed. Technically, gene therapists have proven that ADA deficiency can be treated with gene therapy; commercially, however, it may be an impractical product. Should the government supply this treatment if no pharmaceutical or biotechnology companies are willing to provide it? At what cost? This is particularly relevant given the high priority Congress is putting on cost containment of health care.

On the subject of government regulation of clinical trials and drug approval, I find my experience at Viagene to be somewhat at variance to that of many of my colleagues in biotechnology. Perhaps this is due to our major focus on treatments for HIV infection and cancer. Nevertheless, our company has only compliments to offer about the actions of the FDA. We have been dealing primarily with the Division of Cellular & Gene Therapies, Dr. Phil D. Noguchi, Director, which is part of the Center for Biological Evaluation and Research. We have found them to be rigorous but reasonable. More importantly, they have been very responsive and prompt in their interactions with our company, allowing us to make important decisions or changes quickly, without

compromising the aggressive development schedules we are pursuing for these fatal diseases. Finally, we have found the FDA staff to be scientifically more knowledgeable about gene therapy than other government agencies that have been involved in clinical trial regulation.

In contrast, we have sometimes found the other non-FDA regulators to be capricious, uninformed, and unresponsive. Consequently, we are encouraged and pleased by recent developments that centralize the coordination and regulation of gene therapy clinical trials under the FDA.

In terms of price control issues, the industry wishes to praise the efforts of this Committee and the Technology Subcommittee for the exceptional educational effort it has undertaken during the health care debate. No committee has better understood the role of innovation in improving patient outcomes and lowering health care costs. You have had a real impact in defending health care innovators and for that we are very appreciative.

The position of BIO and the industry on price controls has been that they stifle our ability to raise capital and, therefore, deprive us of the capital we need to fund research. With so few biotechnology companies marketing products, we must rely on investors to fund research and price controls tell these investors that their upside opportunity for profits is limited. Investments in the biotechnology industry are risky enough and price controls fully tip the balance in favor of other investments in less risky ventures which operate in a freer market.

We are sure to see price control proposals again and we hope to work with the Committee to ensure that these proposals do not become law.

In terms of technology transfer, let me say two things. First, many biotechnology companies have been founded around basic research funded by the National Institutes of Health, particularly its extramural program with the universities and foundations. Our ability to transfer basic research to private companies for commercialization is one of the greatest strengths we have and it is vital to American competitiveness. Second, the technology transfer process is threatened by the insistence of NIH on reviewing future product pricing of its CRADA and license partners in its intramural program. This price review process leads many biotechnology companies to refuse to enter into these

agreements and there is a real fear that this price review process will be extended to the extramural program with disastrous results. If this same price review approach were extended to the CRADA and license programs of NTIS or other government agencies, it would be a disaster for the whole technology transfer effort of the government. We recommend that the Committee communicate its concern about the NIH price review policy to NIH, which is currently reviewing this policy.

OUR HOPE FOR THE FUTURE

In closing, I encourage the committee's continued interest in this important frontier of science. Gene therapy is potentially the most effective and longest-term treatment for mankind's most dreaded diseases. Its impact on human health could potentially equal or exceed that of sanitation, antibiotics, or vaccines, which are often named as the most important man-made health contributions of all times. Our country has been blessed with the privilege of leadership in this field. Nevertheless, we should understand that continued leadership is not a right, it must be earned through responsible, thoughtful, and diligent use of this technology. These obligations extend bevond the scientific community into government and industry. If these three constituencies do not in aggregate fulfill our country's obligations, then others will step into the breach.

Viagene feels a sense of obligation to America and its citizens. But we see our obligation as being first and foremost to save American lives and reduce American suffering. Regrettably, if we cannot obtain domestically the capital resources to fulfill this dream, we will do so off-shore. In my view, the current climate in this country, particularly with regard to financing, is incompatible with continued technical leadership in gene therapy. I urge you to provide legislative leadership before we lose control over this important field.

Thank you for your invitation to testify and for your attention. I would be happy to answer your questions.

RECORD #2 OF 2
COMPANY NAME: Viagene, Inc

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R. Jefferson Works, VP and CFO
Bradley B. Gordon, VP, Finance
Donald E. Longernecker, PhD, Sr VP, Operations
Douglas J. Jolly, PhD, VP, Research
David E. Hartnett, VP, QA/QC
Kieron J. Kowal, PhD, VP, Product Development and Manufacturing
John J. Serbin, PhD, Director, Business Development
EMPLOYEES: 125 employees, 24 PhDs, 4 MDs (4/94)
HISTORY: Founded in June 1987
Member--Biotechnology Industry Organization
FACILITIES: 60,000 sq. ft. research laboratory
18,000 sq. ft. corporate administration facility
15,000 sq. ft. pilot production facility
STOCK INFO: NASDAQ--VIGN
IPO--2 mil shares of common stock at $9/share (12/93)
Overallotment exercised for 300K shares (1/94)
Revenue $8.52 mil (1992) compared to $4.611 mil (1991)
Net loss <$3.093 mil> (1992) compared to <$1.95 mil> (1991)
Earnings <loss> per share <$0.49/share> (1992) compared to $0.00/share (1991)
Average shares outstanding 6.272K (1992) compared to 0 (1991)
Total assets $8.171 mil (1992) compared to $6.526 mil (1991)
PRIV PLACE: Equity capital raised is through private placements with venture capital investors and pharmaceutical companies
Raised $7 mil through private placement of Series D preferred stock (8/91)
INVESTORS: Domain Associates
3i Ventures-THREE I VENTURES
Biotechnology Investments, Ltd
Fairfield Venture Partners
Accel Partners
Cable & Howse Ventures
Sorrento Ventures
Advent International
Indosuez Technology Ventures
Chancellor Capital Management
Green Cross Corp
BUS. STRATEGY: Design and develop gene-based drugs and assays for the treatment of viral infections, cancers, and other serious cellular diseases
SUBJECT TERMS: Diagnostics (NEC); Genetic Engineering/Analysis; Allergy/Anti

inflammatory/Autoimmune Therapeutics; Gene Therapy; Drug Delivery/Design/Formulation; Therapeutics (NEC)

AGREEMENTS: Bayer,Factor VIII gene therapy product for hemophilia A,three year development and licensing agreement--Bayer to provide up to $9 mil in up-front license fees, research funding, and milestone payments,(1/93)
Chiron Corp,gene transfer product for the prevention and treatment of cancer, and gene therapy drug-activation technology,R&D agreement,(11/93)
Green Cross Corp,HIV immunotherapeutics,$40 mil R&D and worldwide licensing agreement (4/91), extended agreement for two years,(4/94)
Miles Inc,genetic therapy product for hemophilia A,R&D agreement,(12/92)
US Army,vaccines against malaria and other infectious diseases using gene transfer technology,development agreement--Viagene to receive exclusive rights of first refusal to license any technology resulting from the collaboration,(8/92)

RES & DEV: Projects ranging from therapeutics to clinical assays, including viral and cancer immunotherapeutics and drug potentiating agents, drug carriers, and quantitative assays for direct viral detection and measurement

*PROD. IN DEV: HIV immunotherapeutic drug to deliver a gene sequence for HIV into cells ex vivo, in Phase I clinicals (4/93)
HIV immunotherapeutic via direct injection, in Phase I clinicals (8/93)
HBV immunotherapeutic, in research phase
HSV immunotherapeutic, in research phase
Lymphokine immunotherapeutic for melanoma, in clinicals
Cervical cancer immunotherapeutic, in research phase
Chiron's Aldesleukin (rIL-2) and Viagene's gamma IFN gene therapy product for melanoma, in clinicals (4/94)

COMPANY TYPE: Public

The ability

to produce protein

drugs intracellularly makes possible

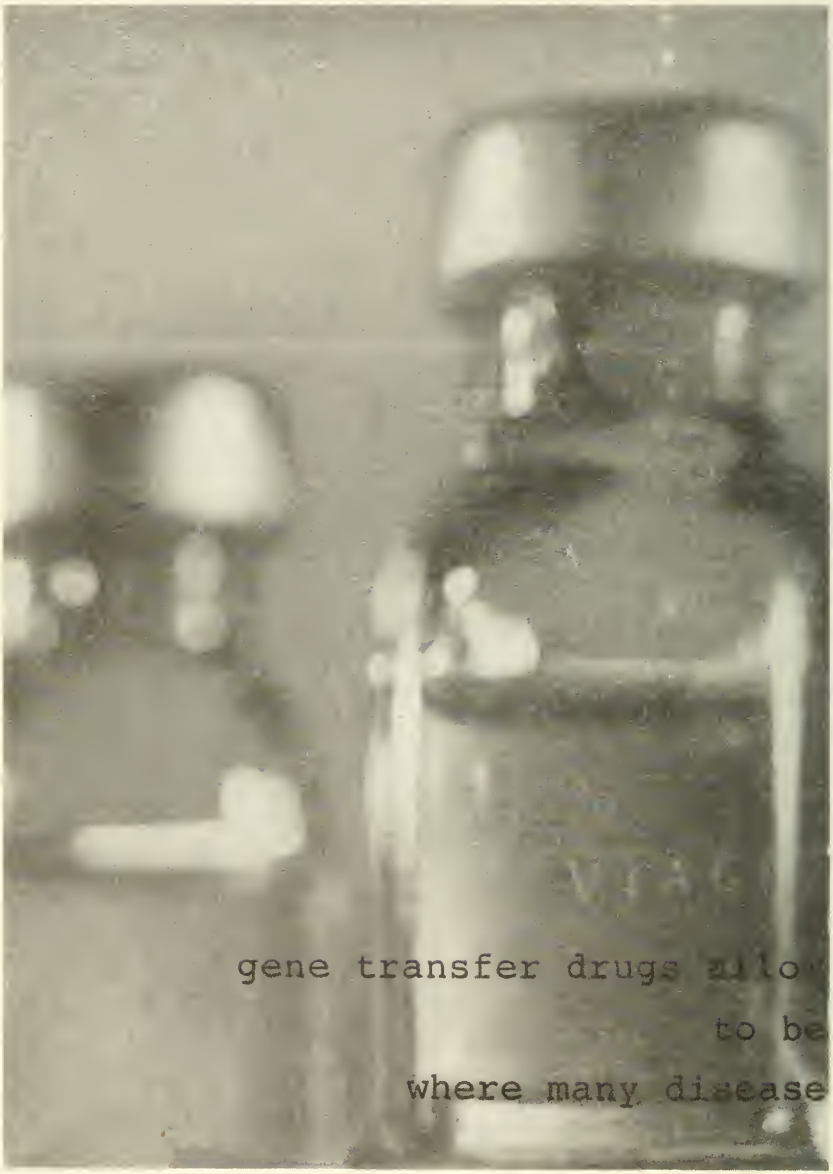
entirely new strategies for managing life-threatening diseases.

Viagene, Inc.

Viagene, Inc.

is a biopharmaceutical company organized to discover, develop, manufacture and market gene transfer drugs for the treatment of viral diseases, cancers and genetic disorders. Founded in 1987, the Company is a pioneer in the emerging field of gene transfer technology. This new technology permits therapeutic proteins to be produced inside of cells, where the majority of disease processes originate. The ability to produce therapeutic proteins intracellularly represents a significant advance in pharmaceutical science that will provide improved methods for the treatment of life-threatening illness. With leading edge technical strength, experienced management and a sound strategic focus, Viagene expects to be among the first companies to bring gene transfer drugs to the market.

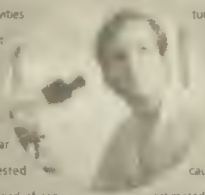

Cell Nucleus
DNA
m-RNA
Ribosome
Protein


gene transfer drugs allo
to be
where many disease

Intracellular Diseases

Today, viral infections and cancers represent two of medicine's most ominous and prevalent clinical problems. Taken together, their morbidity and mortality dwarf any other modern-day disease. Both are intracellular diseases that have in common the ability to seize a host cell's genetic or metabolic machinery in order to replicate and spread in an uncontrolled fashion throughout the body. Genetic diseases represent another class of intracellular diseases. In contrast to viral infections and cancers, genetic diseases usually arise from the failure of a gene to express a normally functioning protein.

Viral diseases and cancers are usually the result of foreign or altered genes becoming active within otherwise normal cells. These genetic-level activities may occur spontaneously, may be inherited, or may occur after exposure to a viral pathogen or environmental pollutant. Clinical disease occurs when these foreign or altered genes disrupt normal cellular functions. In cancer, disease is manifested through the uncontrolled growth and spread of cancerous cells. With viral infections, disease usually results from unchecked growth and replication of progeny virus inside host cells.



Pathogenic Viruses

Viruses are among the smallest known pathogens, far smaller than the cells they infect. A virus is essentially a simple lipid and protein capsule containing a core of genetic material (nucleic acids) and structural proteins. The outer capsule – the envelope – protects the nucleic acid core during transport through the body and mediates the virus' attachment to the surface of target cells. Viruses exert genetic control over host cells as a basic mechanism of survival. Lacking their own reproductive apparatus, they must enter a host cell and utilize its protein-making machinery to manufacture new virus particles. Although most viral infections are short-lived, certain viral infections – such as those caused by the hepatitis B virus (HBV), human papillomavirus (HPV), human immunodeficiency virus (HIV) and herpes simplex virus (HSV) – may result in persistent, lifelong infections because the body's immune system fails to mount an effective response.

Cancers

Like viral diseases, cancers are caused by disruptions in the normal metabolic activity of cells. Scientific evidence suggests that a cell must undergo approximately five distinct genetic alterations before it is transformed into a tumor cell. These genetic changes may arise from a number of different factors, ranging from hereditary and environmental factors to infection by a viral pathogen. Similarities between viral diseases and cancers sometimes extend to a cause-and-effect relationship. Today, an estimated 20 percent of all cancers are associated with viral infections. Examples of cancer-causing viruses include: the hepatitis B virus, associated with liver cancer in chronically infected patients; the human papillomavirus, recently linked with cervical cancer; the Epstein-Barr virus (EBV), associated with certain lymphomas and with nasopharyngeal (nose and throat) cancer; and the human T-lymphotropic virus (HTLV-I), which is believed to be a causative agent in adult T-cell leukemia. Viral infections also are believed to give rise to cancers by suppressing the body's immune defenses. One possible example may be the form of B-cell lymphoma that occurs with high frequency in immune-compromised patients chronically infected by the AIDS virus (HIV).

Gene Transfer Therapeutics

Stored within the nucleus of each human cell is a library of biochemical instructions – genes – that govern all of the body's metabolic activities. Genes are made of DNA (deoxyribonucleic acid), a molecule consisting of long chains of nucleic acid subunits. Acting in concert, genes control the many complex and interrelated functions of cells by serving as blueprints for the production of proteins.

Proteins are essential to all bodily processes, from digestion and food absorption to breathing and blood circulation. When functioning as hormones and enzymes, proteins control a vast array of biochemical reactions. They maintain the delicate internal balance that results in the regulated growth and renewal of cells, the normal functioning of vital organs and glands, and protection of the body from foreign invaders. Because proteins perform so many physiological tasks, their dysfunction can be responsible for numerous disruptions in normal bodily processes. Thus, the majority of human diseases are actually linked to disrupted protein performance.

Currently Available Drugs

Traditional drugs are often small molecules that interact with proteins throughout the body. Such drugs exert physiological activity in one of two ways: they can either enhance or inhibit the normal function of protein molecules. Newer biopharmaceutical products are often large protein molecules that act as replacements for the body's own proteins. However, both traditional drugs and biopharmaceuticals usually function in the extracellular environment, generally interacting with receptors on a cell's outer membrane. A small proportion of existing drugs can efficiently permeate the cell's outer membrane, usually only if they are delivered in high dosages. However, high doses may also lead to toxic side effects.

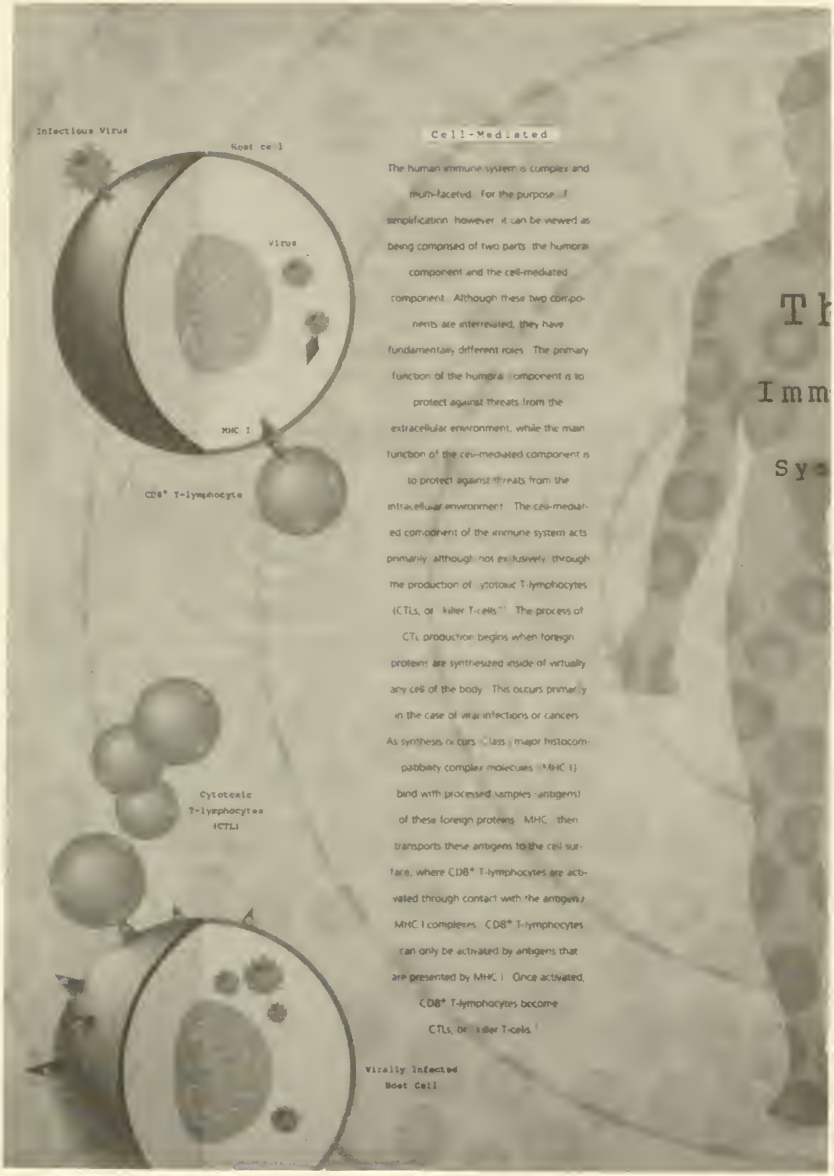
Gene Transfer Drugs

The majority of currently available drugs either are unable to be transported efficiently into a cell's interior, where most disease processes originate, or lack specificity for a particular disease process. The cell membrane has long been a biological barrier to the effective treatment of many diseases, particularly intracellular diseases such as viral infections, cancers and genetic diseases. Now, the advent of gene transfer drugs allows therapeutic proteins to be produced inside cells. This provides an opportunity at the intracellular level to replace or inactivate the effects of disease-causing genes, or to augment normal gene functions to overcome illness. Thus, gene transfer drugs have the potential to treat disease processes at their source.

For example, certain genetic diseases that are caused by a dysfunctional human gene might be treated through augmentation gene therapy. These could include such diseases as hemophilia, emphysema, cystic fibrosis, muscular dystrophy, diabetes type I, and even certain forms of cardiovascular disease. However, the greatest opportunity for early application of gene transfer drugs is in the field of immunology, specifically, by enhancing the body's immune response to disease.

therapeutic proteins
produced directly inside cells,
processes originate

(5)



Cell-Mediated

The human immune system is complex and multi-faceted. For the purpose of simplification, however, it can be viewed as being comprised of two parts: the humoral component and the cell-mediated component. Although these two components are interrelated, they have fundamentally different roles. The primary function of the humoral component is to protect against threats from the extracellular environment, while the main function of the cell-mediated component is to protect against threats from the intracellular environment. The cell-mediated component of the immune system acts primarily, although not exclusively, through the production of cytotoxic T-lymphocytes (CTLs, or "killer T-cells"). The process of CTL production begins when foreign proteins are synthesized inside of virtually any cell of the body. This occurs primarily in the case of viral infections or cancers. As synthesis occurs, Class I major histocompatibility complex molecules (MHC I) bind with processed samples (antigens) of these foreign proteins. MHC I then transports these antigens to the cell surface, where CD8+ T-lymphocytes are activated through contact with the antigen/MHC I complexes. CD8+ T-lymphocytes can only be activated by antigens that are presented by MHC I. Once activated, CD8+ T-lymphocytes become CTLs, or "killer T-cells."

The powerful contribution that gene transfer technology can make to the immunotherapy field can be appreciated fully through examination of today's evolving view of the human immune system. Recent advances in molecular biology and immunology are providing a new understanding of the key elements and functions of the immune system. Scientists have identified specific mechanisms that trigger responses distinctly from either the humoral (antibody) or cell-mediated components of the immune system. This is leading to the development of new and innovative therapeutic strategies to harness the power of the immune system to combat currently untreatable illnesses.

Humoral and Cell-Mediated Immunity

The immune system can be viewed as being comprised of a humoral and a cell-mediated arm or component. The primary products of the humoral component are antibodies, while the primary products of the cell-mediated component are cytotoxic T-lymphocytes (CTLs), or "killer T-cells." Antibodies are effective for neutralizing or tagging viruses and bacteria in the extracellular environment. However, antibodies typically are ineffective in killing whole cells, that is, host cells that are virally infected or cancerous. Consequently, the body relies on CTLs, or killer T-cells, to destroy cancer cells and cells infected by viruses.

Of key significance in immune system regulation is the "major histocompatibility complex" (MHC), molecules formerly known as "transplantation antigens." There are two major types of MHC molecules – Class I and Class II. MHC molecules are essential surveillance elements that give a cell the ability to "present" or "serve up" foreign proteins (antigens) to one or the other of the body's two immune system components. Without MHC molecules, the immune system would be severely restricted in recognizing and responding to anything that is foreign to the body.

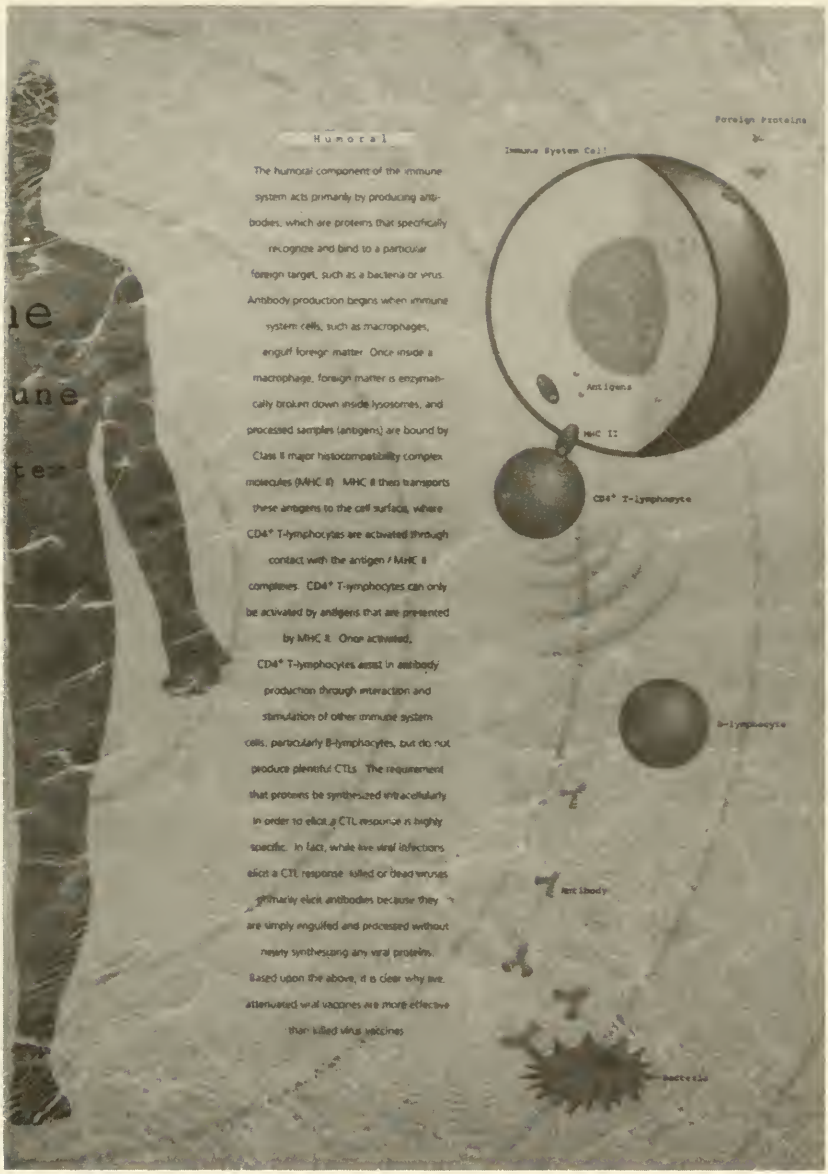
How Antigens Are Recognized

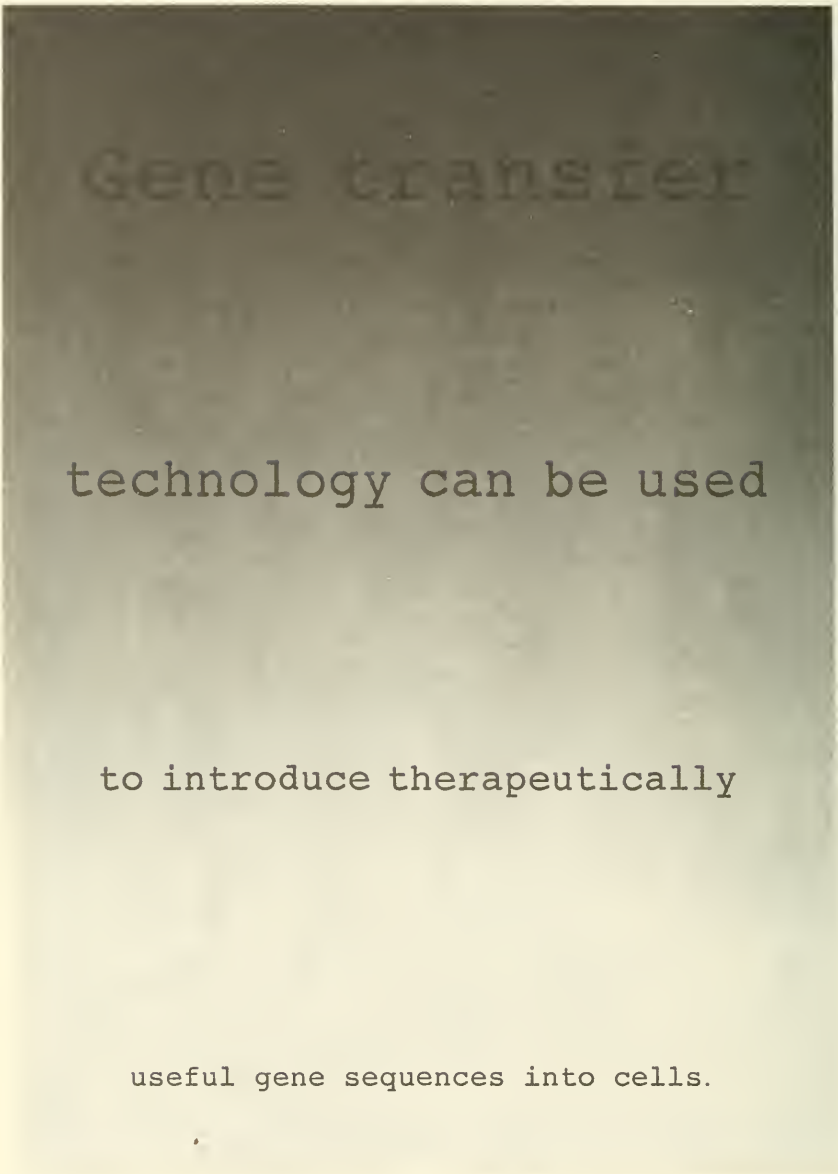
The specific role of each MHC class is related to its functional location within a cell. MHC I molecules reside around the protein factories (e.g., endoplasmic reticulum) of a cell. They monitor the output of these factories and transport processed samples (antigens) of newly produced protein to the cell surface. MHC II molecules, on the other hand, reside in vesicles (lysosomes) that engulf and destroy extracellular materials (such as foreign proteins that bind to the cell's surface). MHC II molecules monitor the contents of these vesicles and similarly transport processed samples (antigens) to the cell surface.

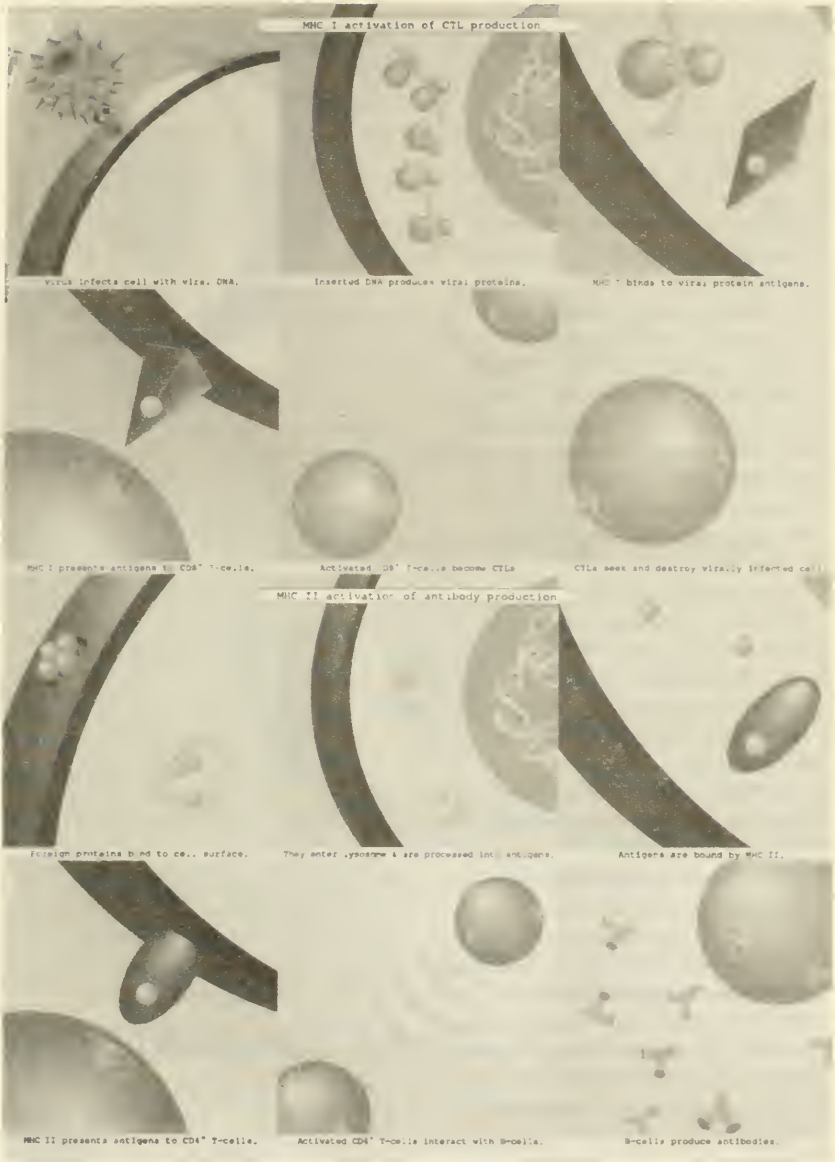
At the cell surface, the two immune system components survey all that is presented by MHC molecules, but with exquisite specificity: the humoral or antibody component can only recognize MHC II-offered samples, while the cell-mediated component can only recognize MHC I-offered samples. This specificity is maintained because of the behavior and function of white blood cells called T-cells, which are integral parts of both the humoral and cell-mediated components of the immune system. In particular, T-cells of the $CD8^+$ subclass, which when activated become CTLs, can only recognize MHC I, while T-cells of the $CD4^+$ subclass, which when activated assist in antibody production, can only recognize MHC II.

Harnessing Cell-Mediated Immunity

Although severe viral infections and many cancers naturally elicit a cell-mediated immune response, the nature of these diseases is to compromise the effectiveness of this response. Many of these diseases are known to suppress the production of MHC I, for example, making it difficult for the immune system to adequately recognize diseased cells. By penetrating the orchestrated intracellular world of MHC, gene transfer drugs are able to vigorously enhance stimulation of the cell-mediated component of the immune system. By producing foreign proteins intracellularly – thereby activating MHC I presentation – gene transfer drugs leverage the specificity and potency of the cell-mediated response of the immune system in combatting cancer and viral diseases.


Humoral
The humoral component of the immune system acts primarily by producing antibodies, which are proteins that specifically recognize and bind to a particular foreign target, such as a bacteria or virus. Antibody production begins when immune system cells, such as macrophages, engulf foreign matter. Once inside a macrophage, foreign matter is enzymatically broken down inside lysosomes, and processed samples (antigens) are bound by Class II major histocompatibility complex molecules (MHC II). MHC II then transports these antigens to the cell surface, where CD4+ T-lymphocytes are activated through contact with the antigen / MHC II complexes. CD4+ T-lymphocytes can only be activated by antigens that are presented by MHC II. Once activated, CD4+ T-lymphocytes assist in antibody production through interaction and stimulation of other immune system cells, particularly B-lymphocytes, but do not produce plentiful CTLs. The requirement that proteins be synthesized intracellularly in order to elicit a CTL response is highly specific. In fact, while live viral infections elicit a CTL response, killed or dead viruses primarily elicit antibodies because they are simply engulfed and processed without newly synthesizing any viral proteins. Based upon the above, it is clear why live, attenuated viral vaccines are more effective than killed virus vaccines.
Foreign Proteins
Immune System Cell
Antigens
MHC II
CD4+ T-Lymphocyte
B-Lymphocyte
Antibody
Bacteria


Gene transfer
technology can be used
to introduce therapeutically
useful gene sequences into cells.


MHC I activation of CTL production
Virus infects cell with viral DNA.
Inserted DNA produces viral proteins.
MHC I binds to viral protein antigens.
MHC I presents antigens to CD8+ T-cells.
Activated CD8+ T-cells become CTLs
CTLs seek and destroy virally infected cells
MHC II activation of antibody production
Foreign proteins bind to cell surface.
They enter lysosome & are processed into antigens.
Antigens are bound by MHC II.
MHC II presents antigens to CD4+ T-cells.
Activated CD4+ T-cells interact with B-cells.
B-cells produce antibodies.

Viagene's Therapeutic Strategy

Viagene's initial focus is the development of immunotherapeutic products that function by "mimicking" disease processes, thereby triggering potent immune responses to intracellular diseases such as persistent viral infections and cancers. These diseases often exist because the body has failed to mount an effective response to a foreign or altered protein.

Activating Cytotoxic T-Cells (CTLs)

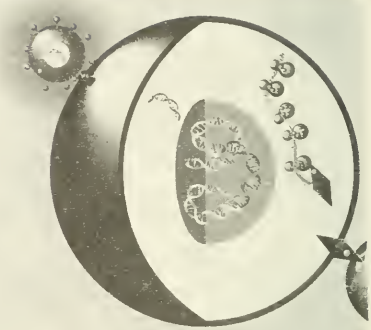
Immunotherapies under development at Viagene are designed to overcome elements of the pathogenic process that allow viruses and cancers to evade detection by the immune system. Viagene's immunotherapeutic drugs work by delivering genes that code for specific foreign or altered proteins. These genes then express the foreign antigens in a manner that mimics infection and optimizes immune recognition and response.

Viagene uses genetically engineered viral vectors (specifically murine retroviral vectors) to deliver gene sequences into cells. This results in the intracellular production of specific proteins, which in turn activates a cytotoxic T-lymphocyte immune response. By contrast, if such proteins would be delivered to the extracellular environment, they would instead be engulfed into the lysosomes of a cell and stimulate an antibody response.

Retroviral vectors facilitate the production of therapeutic proteins without altering or disrupting other normal cell functions. This allows the mimicking of disease processes without any of the immunosuppressive effects associated with natural viral infections and cancers.

HIV Immunotherapeutic

Viagene's lead product is an immunotherapeutic for the treatment of human immunodeficiency virus (HIV) infection, the virus associated with AIDS. The product employs a genetically engineered murine retroviral vector to achieve intracellular delivery of a gene sequence that codes for certain HIV proteins. The resulting intracellular production of these foreign proteins leads to a vigorous response of cytotoxic T-lymphocytes against cells infected with HIV.

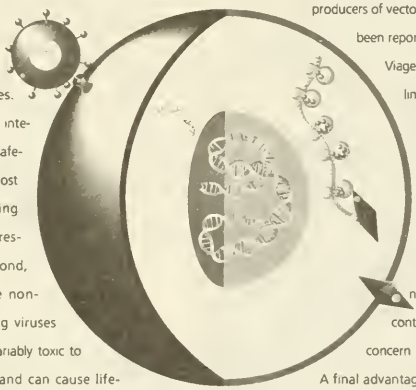


Non-replicating retroviral vectors are used to deliver genetic sequences that encode for selected viral proteins.

the intracellular
foreign
vigorous CTL

Viagene's Gene Transfer Technology

Viagene's gene transfer technology is broadly based and can be applied to develop products for treating not only genetic diseases, but also serious viral infections and cancers. A key element of any gene transfer technology is the method used to deliver therapeutic genes into living cells. Until recently, however, practical or commercially viable methods for introducing genes into cells have not existed. Although there have been a variety of methods available, including both chemical methods as well as the use of bacteria or viruses as delivery vehicles ("vectors"), most methods have had significant disadvantages.



The ideal gene delivery system should have four key features. First, the vector should integrate therapeutic DNA safely and actively into a host cell's genome, ensuring stable, long-term expression of the gene. Second, the vector should be non-replicating. Replicating viruses used as vectors are invariably toxic to the cells they infect, and can cause life-threatening infections in humans. Third, the ideal vector should have a substantial payload capacity, i.e., it should be able to carry genes of varying size. Fourth, the vector should not produce any proteins of its own. These proteins could lead to an extraneous immune system attack on the vector-treated cells that could compromise the effectiveness and safety of subsequent treatments.

Murine retroviral vectors are the only vectors that presently satisfy all of these gene delivery requirements. They can be engineered to be non-replicating, they are not pathogenic to humans, they produce no proteins other than the therapeutic protein of interest, they reliably and efficiently integrate into the host cell's genome, and they can carry over 95% of those genes currently associated with a human disease.

Every major gene transfer company, including Viagene, and the large majority of academic investigators, have selected murine retroviral vectors for use in clinical trials. No other vector system has been shown to be more effective or safer than murine retroviral vectors.

Viagene has distinguished itself among the users of retroviral vectors in two important areas. First, Viagene has developed manufacturing cell lines that are the most efficient producers of vector product of any that have been reported so far. In some instances, Viagene's manufacturing cell lines are between 10-fold and 100-fold more productive than other cell lines. Second, Viagene has created a new type of manufacturing cell line that produces products with no detectable "helper virus" contamination, a common concern in some other cell lines.

A final advantage for using retroviral vectors relates again to the fact that they produce no extraneous proteins. Viagene has used this feature to establish a unique, proprietary assay for functionally measuring the presence of specific CTL responses. Until now, all assays for measurement of specific CTL responses have been indirect and inadequate, leading to confusing claims within the scientific community regarding the effectiveness of various therapeutic vaccines to promote a CTL response.

In summary, Viagene is strongly positioned to be the first gene transfer company to commercialize this important new technology.

production of a protein results in a response

The efficiency of this product in producing a CTL response has been demonstrated in a mouse model and in macaque monkeys, and has now advanced into human clinical trials. Of particular significance is the discovery in laboratory experiments that these CTL responses recognize the various strains or mutations of HIV. Thus, a CTL response that is elicited using a vector product derived from one strain of HIV can recognize and kill cells infected by most, if not all, other strains of HIV. This discovery has been confirmed using human cells infected with live HIV as targets.

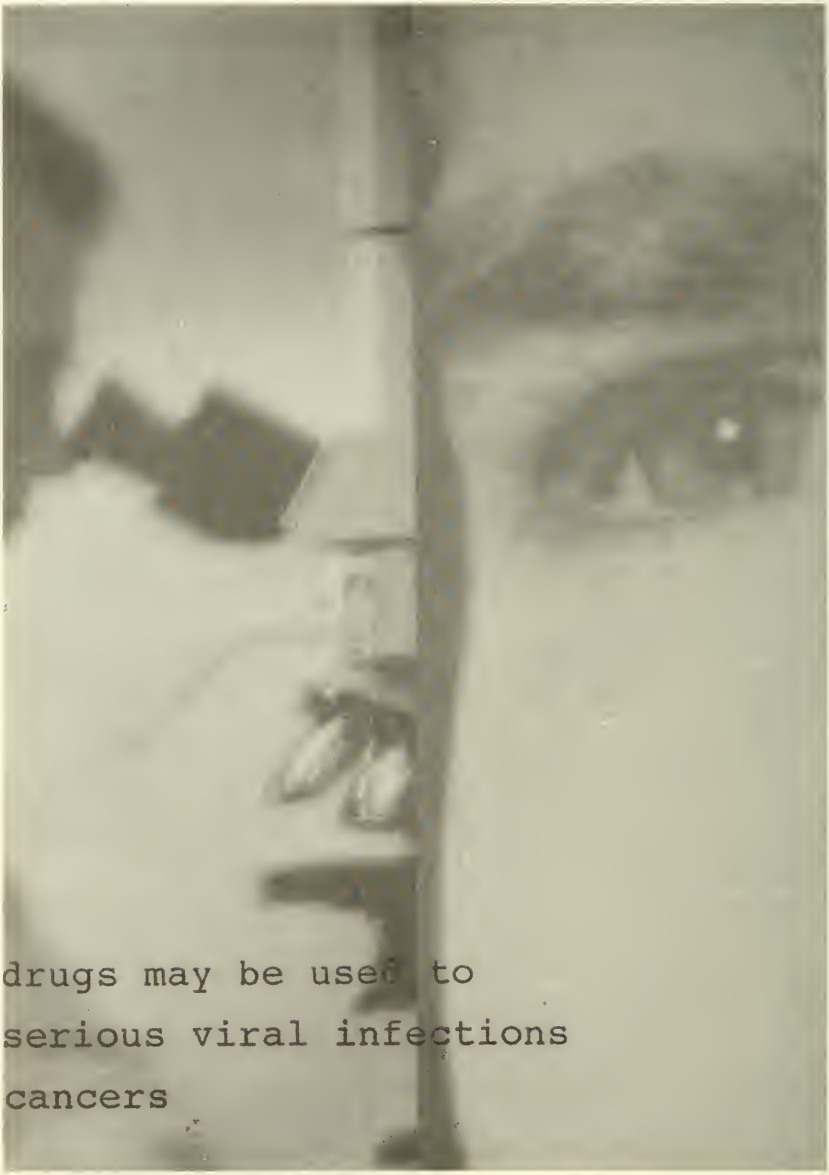
Future Viagene Products

Viagene is initially developing products in what is perhaps the most promising area within the broad arena of gene transfer technology – immunotherapy. The Company's products are designed to tap into the body's existing mechanisms for processing foreign antigens. In doing so, Viagene's products can be used to elicit therapeutic immune responses against a vast array of viral infections and malignancies.

Viruses and cancers share a common property that makes them opportune targets for gene transfer therapeutics. Throughout their life cycle, viruses and cancers produce a number of distinct proteins. Because these proteins are foreign to those normally produced by a cell, they serve as specific "markers" that distinguish diseased from normal cells. Functioning as the body's natural defense mechanism, the immune system has evolved a specialized mechanism to recognize and destroy cells that display foreign proteins produced by viral infection or malignancy. This mechanism is the MHC I-mediated CTL response. Viagene's immunotherapeutic products are designed to assist the immune system in mounting a highly coordinated and specific CTL attack against intracellular disease.

Other Immunotherapeutic Products

The gene transfer technology that Viagene has developed for its HIV immunotherapeutic products holds great promise for the treatment of other serious viral infections, as well as certain


drugs may be used to
serious viral infections
cancers

cancers Viagene's strategy is to apply this gene transfer technology to the treatment of other serious diseases, such as those caused by hepatitis B virus, herpes simplex virus, human papillomavirus and Epstein-Barr virus. The human papilloma and Epstein-Barr viruses are believed to be the causative agents leading to the development of cervical cancer and nasopharyngeal (nose and throat) cancer, respectively Parasitic infections such as malaria and leprosy are also potential targets for Viagene's therapeutic approach.

Viagene's technology may also prove valuable in veterinary medicine There is a great need for effective therapeutic products to treat diseases such as feline immunodeficiency virus (the equivalent of AIDS in cats), equine infectious anemia (a disease of horses), avian flu (a disease of chickens), and visna virus (which affects sheep).

Future Gene Transfer Products

Longer-term, other exciting applications of gene transfer technology also will be realized Through the use of murine retroviral vectors, it will be possible to deliver human gene sequences for the purpose of augmenting or replacing defective human genes that cause disease First among these possibilities will be diseases whose gene products do not require targeting to a specific cell type or location in the body – for example, treatment of hemophilia A through use of the gene sequence for Factor VIII protein. Later, effective treatments for diseases such as diabetes, cystic fibrosis, muscular dystrophy, certain types of emphysema, and certain diseases involving elevated blood cholesterol levels may also be achievable.

In summary, the field of gene transfer technology is opening the door to treatment opportunities that were only dreams just a decade ago.

Glossary

Antigen – a molecule, usually a fragment of protein, that is recognized by the immune system as foreign, or non-self.

Cell-Mediated – occurs through the direct action of cells

CTL (cytotoxic T-lymphocyte) – a T-lymphocyte that kills other cells.

Gene Transfer Technology – the delivery of a functional gene into a living cell.

Lymphocyte – a class of white blood cells that includes two sub-classes, B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

B-lymphocyte – a sub-class of lymphocytes that can produce antibodies

T-lymphocyte – a sub-class of lymphocytes comprised of cell types that have different primary functions For example, $CD4^+$ T-lymphocytes assist in antibody production, whereas $CD8^+$ T-lymphocytes can become CTLs

Major Histocompatibility Complex (MHC) – a system of molecules whose cellular function is to bind and present antigens to the immune system. Has two major classes, MHC I and MHC II.

MHC I – class of MHC that presents antigens to the cell-mediated (CTL) arm of the immune system.

MHC II – class of MHC that presents antigens to the humoral (antibody) arm of the immune system.

Murine – mouse.

Retroviral Vector – type of gene transfer drug that uses a genetically engineered retrovirus as a carrier vehicle to deliver a therapeutic gene into a living cell.

Retrovirus – a type of virus with "RNA genes" whose life cycle after infecting a host cell includes converting its RNA genes into DNA genes, which are then inserted into the chromosomes of the cell it has infected

Agency: Noonan / Russo Communications Design: Diane DeLucia Design, NYC
Illustration: MicroColor Inc. Photography: Bard Martin (Pg 14,15), Earl Ripling (Pg 4) Printer: Diversified Graphics Inc

Mr. VALENTINE. Thank you, sir. I thank all of you.

Well, let me kind of start my questions at the end. From the testimony, especially of Mr. Abbott and Dr. Swarz, about this situation that has affected the flow of capital to these—into these speculative enterprises, I know you are talking about of course the efforts of health care reform.

But in all fairness, wasn't capital a problem before this Administration began to move health care reform up to the top burner on the stove? I mean, is that all the problem?

Mr. ABBOTT. No, certainly not. As you will find in my written testimony, the—

Mr. VALENTINE. Excuse me. I will come back there. How about you, Dr. Swarz? Is that all the problem? You seem to be pretty tough on this.

Mr. SWARZ. No, it is not all the problem, Mr. Valentine, but up until February of 1993, capital had been readily available in the equity markets for most biotechnology offerings, new company offerings, entrepreneurial offerings. One might argue that there was some excess in the marketplace and that some companies that went public and raised money shouldn't have raised money but, for the most part, the capital was available.

When it became clear early in the current administration's start after the President took office that what the health care policy—health care reform would look like that indeed price controls were going to be part of that policy, and that the President and his colleagues and Mrs. Clinton vocally went after the pharmaceutical industry on price, it had a demonstrative chilling effect on the prices, current daily prices of all drug companies, major pharmaceutical firms and on the prices of biotechnology stocks and they began to decline precipitously.

Mr. VALENTINE. They should have concentrated on insurance companies. Anyway, I don't want to—you know, I understand what you are saying and I—but I know that none of you are saying that in an effort to do something about a terrible problem in the country and that's health care. I mean, nobody in their right minds wants to do anything that would adversely affect the quality.

In my district, probably we might come behind California and New Jersey in the number of pharmaceuticals Research Triangle Park and elsewhere in that district—and so that has been for me a political problem as well as for others, but I hope we are not saying that when we address the problem of how to create a situation in this country, that we can have a minimum amount of government interference or government meddling and do something to try to bring the costs down.

My God, to go to the hospital now, one of those little country hospitals and stay overnight, 3,000 bucks. We don't want to create a situation, I hope, where any segment of this industry is off limits.

Mr. SWARZ. Congressman, I agree with you and it isn't off limits and I do not mean to give that impression. However, I think it is a mistake to assume that if one controls or puts a price control on what is effectively 7 percent of a trillion-dollar expense and makes the assumption that controlling that 7 percent and bringing it down to 4 percent of a trillion-dollar expense is going to have any

meaningful effect on the overall cost of health care is frankly living in a gilded cage. I mean, it is not going to happen.

And I think what people on Wall Street said, that if government is going to go after that 7 percent of a trillion-dollar business, that they are making a mistake and investors, again, are trying to minimize risks. No one wants to fight the U.S. Government and they avoided the stocks.

Mr. VALENTINE. Well, you can't really tell what causes Wall Street to be scared, can you?

Mr. SWARZ. Well, that's true, you can't.

Mr. VALENTINE. I didn't mean to cut you off, Mr. Abbott. I will come back to you and I am laboring under some constraints myself. I don't mean to suggest that this, my presiding today is too much of a good thing, but I was—I didn't know I was going to have this much of an opportunity and I have run into some problems, I have a constituent meeting, so I am going to have to wrap this up and ask you to respond to questions that we send to you, perhaps. But, Mr. Abbott, I did cut you off so go ahead.

Mr. ABBOTT. Actually, First Boston was our banker and I think he's represented what I would have said.

Mr. VALENTINE. I was going to ask him a while ago if he's a doctor doctor or a money doctor. We need both.

Well, I will just ask one question then. I do want to have Dr. Walters comment briefly on what he sees as the ethical issues involved in the testing in humans, human trials.

Mr. WALTERS. Are you referring to gene therapy that doesn't involve reproductive cells, that only involves the patient's own cells in an attempt to treat that patient's disease?

Mr. VALENTINE. That first and the other next.

Mr. WALTERS. All right. With the treatment of the patient's own cells and no attempt to pass changes on to the patient's descendants, I think the issues are very similar to those that one would face with testing any new drug or new device or new vaccine. There is a safety question. We want to be sure from preliminary studies that patients are not likely to be hurt. There's also a question of good design and an adequate science base so that there is a reasonable hope of getting reliable results from the study.

And then I think the question of good disclosure and an informed consent by the participants is very important. I am sad to say that even after local institutional review boards have reviewed consent forms for many of the gene therapy studies, we still have to do major surgery on those consent forms to simplify them and to make very clear what the goal of initial gene therapy studies will be.

Mr. VALENTINE. Okay. As I stated earlier, we might have questions from Members who are not here, those who have been here and had to depart. And we would appreciate it within reason if you would respond to those.

And let me, as we have said to the other panels, thank you very much for your words of wisdom.

Thank you.

And with that, the committee is adjourned.

[Whereupon, at 4:48 p.m., the committee was adjourned.]

APPENDIX

federal register

Thursday
October 14, 1993

Part II

Department of Health and Human Services

Food and Drug Administration

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice

autologous bone marrow transplantation employing bone marrow enriched for stem cells by immunoadherence. (However, extensive manipulation of bone marrow for the purpose of obtaining purified stem cell populations would result in a somatic cell therapy subject to licensure.)

B. Gene Therapy

1. Definition

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration or may be altered in vivo by gene therapy products given directly to the subject. When the genetic manipulation is performed ex vivo on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.

2. Final Products Containing the Genetic Material Intended for Gene Therapy

Final products containing the genetic material intended for gene therapy are regulated as biological products requiring PLA's (e.g., viral vectors containing genetic material to be transferred, ex vivo transduced cells and analogous products) or as drugs requiring NDA's (e.g., synthetic products) regardless of whether they are intended for use in vivo or ex vivo. Gene therapy products that are licensed biological products intended for further manufacture if they are intended to be used ex vivo during the manufacture of genetically altered cells.

Examples include the following: (1) A synthetic polynucleotide sequence intended to alter a specific genetic sequence in human somatic cells after systemic administration is regulated as a drug requiring an NDA; (2) a retroviral vector containing the adenosine deaminase (ADA) gene, intended to be administered intravenously to the patient, is regulated as a biological product requiring a PLA; and (3) a retroviral vector containing the ADA gene and intended to modify cells ex vivo is regulated as a biological product intended for further manufacture requiring a PLA.

3. Viral Vector Systems Intended for Further Manufacture Into Final Products

The manufacture and quality control of viral vector systems (i.e., not containing the complete genetic material) that are designed to serve as the starting point for further manufacture into final products (i.e., insertion of additional genetic material into the vector) may be described in a drug master file.

C. Ancillary Products Used during Production of Somatic Cell Therapies

Numerous products will be used during production of somatic cell therapy. Examples include the following: (1) Bioreactors and cell culturing systems, (2) components of culture media, (3) drug- or biologic-like components used to activate or otherwise change the biological characteristics of the cells, (4) certain antisense polynucleotides, and (5) agents used to purge or select or stimulate specific cell populations. A common characteristic of these products is that they are intended to act on the cells, rather than to have an independent effect on the patient. Additionally, the intended action of these products is not dependent upon incorporation into the somatic cell with maintenance of the products' structural or functional integrity.

These products meet the definition of medical devices. They are regulated as devices, with the type of regulatory control being determined according to codified procedures. In contrast, products administered directly to patients or products whose function requires incorporation into the somatic cells with maintenance to some degree of structural or functional integrity (e.g., viral or other vectors containing genetic material to be used in gene therapy) are not considered ancillary products; rather, they are regulated as drugs or biological products.

The center primarily responsible for regulating a particular device will be designated according to the current interagency agreements. For example, according to the current agreement, CDER will regulate the synthetic antisense compounds. CBER will be responsible for monoclonal antibody-based purging agents, and CDRH will oversee the approval of bioreactors.

D. Combination Products

Many somatic cell products administered to patients will be combinations of a biological product and a device or of a drug, a biological product, and a device. Examples include the following: (1) Encapsulated pancreatic islet cells secreting insulin and (2) a device containing encapsulated cells secreting a neurotransmitter. The combination products for which the primary mechanism of action is that of the somatic cell therapy component will be regulated as biological products.

IV. Comments

FDA recognizes that somatic cell and gene therapy products constitute a new and emerging scientific area. The agency will review and consider written comments on the regulatory approach set forth in this notice. Any comments received will be considered in determining whether amendments to, or revisions of, the approach are warranted. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments received are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 24, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93-24938 Filed 10-13-93; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93N-0173]

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice

SUMMARY: The Food and Drug Administration (FDA) is making available, through this document, a statement of the manner in which FDA's current statutory authorities governing therapeutic products apply to human somatic cell therapy products and gene therapy products. FDA is publishing this statement in response to requests that the agency clarify its regulatory approach and provide guidance to manufacturers of products intended to be used in somatic cell therapy or gene therapy. As scientific knowledge in the area of somatic cell and gene therapy continues to accumulate and evolve, the agency's approach may also evolve.

DATES: Submit written comments on the document by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Submit investigational new drug applications (IND's) for somatic cell therapy and gene therapy products to the Division of Application Review and Policy (HFM-585), Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Submit written requests for single copies of the document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" to the Congressional and Consumer Affairs Branch (HFM-12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-295-9000. Send two self-addressed adhesive labels to assist that office in processing requests.

FOR FURTHER INFORMATION CONTACT: Ann Reed Gaines, Center for Biologics Evaluation and Research (HFM-635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

As a consequence of scientific and biotechnological progress during the past decade, new therapies involving somatic cells and genetic material are being investigated, and commercial development of products for use in somatic cell therapies and gene therapies is occurring. Existing FDA statutory authorities, although enacted prior to the advent of somatic cell and gene therapies, are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing. Manufacturers and other interested parties have questioned FDA regarding how such products will be regulated. This statement outlines the current regulatory approach to products intended for use in somatic cell and gene therapies.

II. Background

A. Legal Authorities

FDA regulates numerous kinds of products intended to prevent, treat, or diagnose diseases or injuries under legal authorities established in the Public Health Service Act (the PHS Act) and the Federal Food, Drug, and Cosmetic Act (the act). Section 351(a) of the PHS Act (42 U.S.C. 262(a)) identifies a biological product as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." Section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) defines the term "drug," in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." The term "device" is defined in section 201(h) of the act, in part, as:

> * * * an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article * * * intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, * * * which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Both the "drug" definition and the "device" definition also include articles "intended to affect the structure or any function of the body."

Section 351(a) of the PHS Act requires premarket approval for biological products. Licenses are to be issued upon a showing that the establishments and products "meet standards, designed to insure the continued safety, purity, and potency of such products * * *." (42 U.S.C. 262(d)). A biological product's effectiveness for its intended uses must be shown as part of the statutory requirement for potency (21 CFR 600.3(s)). At the investigational stages, when the products are being studied in clinical trials to gather safety and effectiveness data, biological products must meet the requirements of part 312 (21 CFR part 312). FDA's biologics regulations require the submission of both product license applications (PLA's) and establishment license applications (ELA's) (21 CFR 601.1 through 601.10). Biologics establishments and products must satisfy detailed standards set forth in the regulations (21 CFR parts 600 through 680).

Section 351(b) of the PHS Act prohibits falsely labeling or marking a biological product. Under section 361 of the PHS Act (42 U.S.C. 264), the agency may promulgate regulations to prevent the introduction, transmission, or spread of communicable diseases.

Products considered to be biological products subject to the provisions of section 351 of the PHS Act are simultaneously also drugs or devices subject to the applicable provisions under the act. For example, the adulteration, misbranding, and registration provisions of the act would apply to the product as a drug or device.

Under section 501 of the act (21 U.S.C. 351), both drugs and devices are considered adulterated for any of a number of specified reasons. Included among these adulteration provisions is the requirement that the methods and facilities and controls used for manufacture, processing, packing, and holding or installation conform with current good manufacturing practice (CGMP) regulations (21 U.S.C. 351(a)(2)(B) and (b)). FDA's implementing regulations codified at 21 CFR parts 211 and 820 specify the drug and device CGMP requirements.

Section 502 of the act (21 U.S.C. 352) sets forth misbranding provisions that apply to drugs and devices. Among other circumstances, a drug or device is considered misbranded if the labeling is false or misleading or if the labeling fails to bear adequate directions for use or adequate warnings against unsafe use (21 U.S.C. 352(a) and (f)). Any drug or device is also misbranded if it is dangerous to health when used in the manner or with the frequency suggested in the labeling (21 U.S.C. 352(j)). For prescription drugs and restricted

devices, section 502 of the act describes certain information that must be included in all advertisements or other printed material (21 U.S.C. 352(n) and (r)). FDA's regulations also establish labeling and advertising requirements in more detail (21 CFR parts 201, 202, and 801).

Section 510 of the act (21 U.S.C. 360) requires persons who own or operate establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices (with certain exceptions) to register those establishments with FDA. Individuals who must register their establishments under section 510 of the act must also file a list of all the drugs and devices being made or processed at the establishment. FDA's registration regulations are codified at 21 CFR parts 207 and 807.

Although products regulated by FDA as biological products must also meet drug or device requirements, the agency does not require duplicate premarket approvals. For example, if FDA requires a PLA to be submitted for the product as a biologic, the agency does not also require submission of a new drug application (NDA) or a device premarket approval application (PMA).

The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biologics and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the act (21 U.S.C. 352(f)(1); 21 CFR 201.5, 201.100(c)(2)). Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)). The act contains a presumption of interstate commerce for devices (section 709 of the act (21 U.S.C. 379e)).

Both the PHS Act and the act provide authority for enforcement of the various statutory requirements. FDA is authorized to conduct inspections to determine compliance with regulatory requirements (42 U.S.C. 262(c) and 21 U.S.C. 360(h) and 374). Approved PMA's may be suspended or revoked (42 U.S.C. 262(a) and 21 U.S.C. 355(e) and 360e(e)). Biological products and devices may be recalled under certain circumstances (42 U.S.C. 262(d)(2) and 21 U.S.C. 360h). Judicial actions, including seizures, injunctions, and criminal prosecutions, may also be initiated (42 U.S.C. 262(f) and 21 U.S.C. 332, 333, and 334).

Some products may contain a combination of biological products and drugs or devices. Under a provision of the Safe Medical Devices Act of 1990, FDA determines the primary mode of action of the combination products (21 U.S.C. 353(g)), then assigns the primary jurisdiction for review of the product within the agency based on that determination. FDA has established procedures for designating the organization within FDA (i.e., the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH)) to review combination products or any other products where the agency center with primary jurisdiction is unclear (21 CFR 3.1 through 3.10). CBER, CDER, and CDRH have also entered into interconter agreements to clarify the centers' responsibilities for reviewing various kinds of products.

B. Regulation of Somatic Cell and Gene Therapy Products

This statement is intended to present the agency's current approach to regulating somatic cell and gene therapy products. For the purpose of this statement, somatic cell therapy products are defined as autologous (i.e., self), allogeneic (i.e., inter-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. Cellular products intended for use as somatic cell therapy are biological products subject to regulation pursuant to the PHS Act (42 U.S.C. 262) and also fall within the definition of drugs in the act (21 U.S.C. 321(g)). As biological products, somatic cell therapy products are subject to establishment and product licensure to ensure product safety, purity, and potency. At the investigational stage, these products must be in compliance with part 312. Clinical trials are, therefore, to be conducted under IND's. As drugs, somatic cell therapy products are also subject to drug requirements such as conformity with CGMP regulations.

FDA has not required premarketing approval for many types of transplantation, including bone marrow transplants. However, recent scientific and biotechnological developments now enable bone marrow to be manufactured into a somatic cell therapy product. Such products are subject to FDA regulation consistent with the approach to other somatic cell therapies described in this statement. In addition, other forms of transplantation, such as the transfer of whole organs and tissues, have been, or are currently being reassessed and addressed by FDA or other Federal agencies in light of current knowledge and technological advances.

Gene therapy products are defined for the purpose of this statement as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products (e.g., those containing viral vectors) to be administered to humans fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act. Other gene therapy products, such as chemically synthesized products, meet the drug definition but not the biological product definition and are regulated under the relevant provisions of the act only.

Biological products intended for use as source materials for further manufacture into licensed somatic cell therapy products or gene therapy products require premarketing approval as biological products intended for further manufacture when they are shipped from one legal entity to another. Such products would be considered part of a shared manufacturing arrangement in which: (1) Two or more manufacturers perform different aspects of the manufacture of a product, (2) neither performs nor is licensed to perform all aspects of the manufacture, and (3) each manufacturer holds product and establishment license applications. In a shared manufacturing arrangement, FDA accepts only license applications for biological products intended for further manufacture that specify the licensed manufacturer or manufacturers to which the intermediate product will be shipped and approves such applications only after demonstration of safety and efficacy of the end product. For example, biological gene therapy products intended for use ex vivo in the manufacture of genetically altered cells for somatic cell therapies will require premarketing approval as biological

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SPECIAL ARTICLE

REGULATION OF SOMATIC-CELL THERAPY AND GENE THERAPY BY THE FOOD AND DRUG ADMINISTRATION

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SCIENTIFIC advances in the past decade have made the clinical testing of somatic-cell therapy and gene therapy a reality. Early trials in humans suggest that important new diagnostic and therapeutic tools are on the horizon. The objectives of this article are to examine the regulation of somatic-cell and gene therapy by the Food and Drug Administration (FDA) in the context of the agency's traditional role in the development of biologic products and to stimulate discussion in areas in which policy is still being formulated.

The technology of somatic-cell and gene therapy has moved from the bench to clinical evaluation with considerable speed. One striking aspect of current and planned clinical trials is the breadth of proposed indications. The flexibility of these new forms of technology allows the rapid tailoring of products for a variety of applications, including use as vaccines, diagnostic agents, drug-delivery systems, and treatments for malignant, infectious, and genetic diseases, as well as for organ failure. Gene therapy and somatic-cell therapy are discussed together here because of their close medical, scientific, and regulatory connection. Of 46 gene-therapy proposals reviewed by the FDA through mid-1993, 38 involved the ex vivo treatment of somatic cells with a gene-therapy vector, followed by the administration of the modified cells to the patient; only 8 involved direct administration of the vector.

Somatic-Cell Therapy

The FDA defines somatic-cell therapy as the administration to humans of autologous, allogeneic, or xenogeneic living somatic cells that have been manipulated or processed to change their biologic characteristics.[1] The cellular products used in somatic-cell therapy meet the statutory definition of biologic products and are subject to regulation by the FDA under the Public Health Service Act.[2] These products also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act and are subject to applicable provisions of that law.[3]

Forms of somatic-cell therapy that are currently being studied include a wide spectrum of interventions. One approach involves expanding or activating autologous cell populations ex vivo. Clinical trials are being conducted at the National Cancer Institute to evaluate the use of tumor-infiltrating lymphocytes that have been expanded and activated ex vivo to treat patients with advanced cancers.[4] The use of activated T lymphocytes has been proposed as a new form of antiviral therapy to treat cytomegalovirus and other viral infections.[5] Ex vivo expansion of other cell types — e.g., autologous bone marrow progenitor cells — is also being attempted. A second approach to somatic-cell therapy involves the use of allogeneic or xenogeneic cells for replacement therapy. This includes the treatment of congenital or acquired diseases such as hemophilia, Parkinson's disease, and diabetes mellitus that are characterized by the deficient production of secreted factors. Rejection of the therapeutic cell population, the principal obstacle to this approach, has been overcome in animal models by the use of semipermeable barriers such as microcapsules or hollow-fiber culture systems. Many additional types of somatic-cell therapy, including partial organ regeneration or supplementation, are in the early stages of exploration.

Gene Therapy

Gene therapy encompasses interventions that involve deliberate alteration of the genetic material of living cells to diagnose, prevent, or treat disease. The administration of cells that have undergone ex vivo genetic manipulation is considered a combination of somatic-cell therapy and gene therapy.[6] Although the majority of human gene-therapy trials to date have used this combination approach, gene-therapy products have also been administered directly to subjects to modify cells in vivo.

Current approaches to gene therapy use modified or attenuated viruses as vectors to carry the genetic material into the cell. Gene-therapy products based on viral vectors meet the statutory definition of biologic products and are subject to regulation by the FDA.[2,3] Other gene-therapy products that are under development use other delivery methods: DNA–liposome mixtures, directly administered DNA, and DNA combined with a targeted delivery system (e.g., a monoclonal antibody or cellular-receptor–targeted ligand–DNA conjugate). These products will also be regulated by the FDA.

Other gene-therapy interventions are also under clinical investigation. One application involves inserting a functional version of a missing or defective gene into a patient's cells. A number of such therapies for congenital genetic diseases are in the late preclinical

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stages of development. A clinical trial is currently evaluating the genetic treatment of severe combined immunodeficiency caused by insufficient adenosine deaminase. Preliminary results of this study, being conducted by Michael Blaese and coworkers at the National Institutes of Health, indicate that T lymphocytes transduced ex vivo with a retroviral vector containing the normal human adenosine deaminase gene have at least temporarily improved patients' immune function.[7,8] Other clinical trials are exploring the feasibility of inserting the cystic fibrosis transmembrane reporter gene by direct inoculation of patients' respiratory epithelium.

A conceptually quite different application of gene therapy involves using lymphocytes to target cytokine delivery to specific sites. Another use is to mark cells to measure their in vivo distribution and persistence.[9,10] An additional application involves creating individualized vaccines by modifying autologous cells to stimulate an effective immune response more efficiently through mechanisms such as the expression of new antigens on the cell surface, the secretion of certain cytokines, or both. This approach is being investigated to treat cancer and chronic infections such as human immunodeficiency virus (HIV) infection. A final example involves introducing a gene into tumor cells to render them susceptible to a drug.[11] Other genetic manipulations targeting diseases as disparate as atherosclerosis and hemophilia are undergoing preclinical testing.[12]

Trials currently under way are unlikely to define the ultimate role of somatic-cell and gene therapy in clinical medicine. As more is learned about the genetic control of growth and differentiation, as well as about genetic mechanisms of pathogenesis, an even broader range of approaches to the diagnosis, prevention, and treatment of disease will undoubtedly come under clinical evaluation.

Clinical Development of Biologic Products

Products that appear promising in early clinical trials of somatic-cell or gene therapy will usually enter a commercial development process with two important parallel components. The safety and efficacy of the products are tested in clinical trials of appropriate design. Concurrently, the manufacture and testing of the biologic product itself are refined to permit large-scale production and distribution of a pure material with reproducible qualities. Although the clinical aspect of this process is the focus of public attention, the product-development component is equally important.

The need for appropriate control of biologic products has been recognized since their first large-scale use in the late 19th century. Therapeutic antiserums were found to be effective in treating certain infectious diseases, but their potency and purity varied widely. In 1901, 13 children in St. Louis died of tetanus after they had been injected with diphtheria antitoxin. Their deaths were traced to tetanus contamination of the equine serum from which the antitoxin was prepared.[13] This and other less dramatic incidents led to the enactment of the Biologics Control Act of 1902 — also known as the Virus, Serum, and Toxin Act — which mandated the federal regulation of biologic products.[14] Since that time, the manufacturers of biologic products have been required to hold licenses both for the product and for all manufacturing facilities.

The control of biologic products has been progressively refined since the 1902 act was passed. Three principles are central: control of the biologic source or sources, control of the production process, and control of the bulk and final product. These principles have been successfully applied to quality control for products as diverse as human blood and vaccines against viruses, and they are also crucial to controlling the quality of products for somatic-cell and gene therapy.

Products for somatic-cell and gene therapy may be derived from a variety of biologic sources, including directly harvested autologous, allogeneic, or xenogeneic cells; cultured cell lines; genetically modified cell lines; and viral vectors. Product safety requires that such sources be well characterized, uniform, distinguishable from the sources of similar materials, and not contaminated by hazardous adventitious agents. At the time of the 1902 act, the control of biologic materials centered around microbiologic testing and animal husbandry. The importance of such controls was illustrated when foot-and-mouth disease occurred in animals used to produce smallpox vaccine.[15] Subsequently, the development of new forms of technology, beginning with the production of viral vaccines by tissue culture, generated additional scientific challenges. Viral seed-lot systems, which set the permissible number of passages from the well-characterized parent virus through vaccine production, were developed to control potential reversion to virulence by attenuated viral strains. In addition, the concept of the production-cell substrate, a defined cellular source material used to produce biologic agents, was developed. Strategies were devised to test for contaminants originating in cell substrates — for example, the simian virus 40 found in the monkey-kidney-cell cultures used to produce poliovirus vaccine. Adventitious viruses continue to be a problem in today's cell substrates. Currently, cell-banking and testing algorithms are used to evaluate the cell substrates used in the production of biologic agents such as vaccines, monoclonal antibodies, and recombinant-DNA products, as well as certain forms of somatic-cell and gene therapy.

Cells directly removed from humans may be used in somatic-cell and gene therapy and pose additional problems in preventing source-related contamination by adventitious agents. Safety issues related to the use of fresh cells first emerged with the advent of blood transfusion. Banking blood for transfusion saved countless lives during World War II, and whole blood subsequently became the first cellular material

approved as a biologic product by the FDA. However, the widespread use of a human-derived cellular product raised unique issues of quality control related to the transfusion-associated transmission of disease. Because blood could not be sterilized by filtration or other means, the development of strategies to control or prevent viral and bacterial contamination was essential. As a result, the evaluation of donor health through history taking, physical examination, and laboratory testing became central to protecting the safety of the blood supply. The recent emergence of HIV reinforces the importance of donor screening and testing procedures when human-derived biologic materials are used.

The concept of controlling the manufacturing process is the second cornerstone in ensuring the quality of biologic products. Rigorous control of the process is essential because of the difficulties inherent in assessing and controlling the consistency of biologic products. Source materials, such as cells, viruses, and blood, are often not uniform. In addition, seemingly minor changes in the conditions of cell cultures or in purification processes may significantly alter the biologic characteristics of the final product. Because of the complex nature of final products that consist of cells, microorganisms, or macromolecules, testing of final products alone cannot reliably detect, test, or control for variability. Manufacturers must therefore rely on controlled, reproducible manufacturing procedures and environments to produce a uniform product. The degree of reliance on a controlled process varies according to the nature of the product. For example, in the case of certain products containing living cells that may be prepared in single-donor, single-recipient batches, the small size of each batch and the need for timely administration of the cells impose special limitations on testing. As a consequence, control over the process and the facility has been particularly emphasized.

The third central principle of controlling biologic products involves control of the bulk and final product. Because the complete chemical characterization of biologic products is not ordinarily feasible for quality control, the testing of biologic potency receives particular emphasis. Controlling the potency of somatic-cell therapies will be particularly challenging and will probably require the development of new approaches.

As the preceding examples demonstrate, control of the production of biologic agents has had a key role in quality assurance from the earliest biologic therapeutic agents through today's scientifically complex interventions. The technical standards developed for the commercial production of somatic-cell and gene therapy will be based on these existing manufacturing and control principles.

The Approach to Regulation

The FDA is responsible for developing a regulatory framework and technical standards for products used in somatic-cell and gene therapy that apply the principles of product control discussed above. Technical requirements are less stringent in the early phases of clinical investigation and become more rigorous during later development.

The Investigational Phase

Clinical studies of investigational biologic agents are performed under an Investigational New Drug (IND) application filed with the FDA. IND applications for somatic-cell and gene therapy must contain information on product manufacturing and testing to ensure that trial subjects will not be exposed to an unreasonable and important risk of illness or injury. For example, an IND application for a gene therapy mediated by a retrovirus vector would be expected to contain detailed information on the molecular biology of the vector and insert, the production and testing of the producer cell banks, safety testing of the final viral supernatant used for transduction of the patient's cells, and any relevant safety or activity testing in animals. Specifications and required testing at each step of the production process would also be submitted.

Cells for somatic-cell therapy are distinguished from cells used for tissue transplantation for regulatory purposes, and questions about the distinction frequently arise. The extent and intent of the cell processing are one factor used in making this distinction. Ex vivo cell processing that involves expansion, selection, encapsulation, or pharmacologic treatment is viewed by the FDA as a manufacturing step that results in a product for somatic-cell therapy. Similarly, processing that alters the biologic characteristics of the cells — i.e., by inserting genetic material, inducing differentiation or activation, or causing the secretion of biologically active factors — defines the result as a product for somatic-cell therapy. However, unmodified autologous or allogeneic bone marrow cells intended for transplantation are not considered regulated products for somatic-cell therapy. Likewise, marrow purged of tumor cells or mature lymphocytes by monoclonal antibodies or drugs will not be considered products for somatic-cell therapy without further modification of the marrow, although the purging agents require FDA approval. In contrast, highly processed marrow cells, such as stem cells selected and expanded ex vivo, will be regulated as products for somatic-cell therapy. Similarly, genetically modified cells, such as transduced autologous hepatocytes, will be considered products for somatic-cell therapy. Issues concerning the regulation of tissue transplantation are under consideration by the FDA as a separate matter.

The Recombinant DNA Advisory Committee of the National Institutes of Health oversees investigational gene-therapy protocols that have received federal funding or are performed at institutions receiving federal funding. The committee and the FDA have important, complementary functions. Review by the committee ensures broad public discussion of the sci-

entific evaluation of this new technology, particularly with regard to social and ethical concerns. The FDA focuses on the development of safe and effective biologic products, from their first use in humans through their commercial distribution. Products used in protocols subject to review by the Recombinant DNA Advisory Committee must also undergo FDA review; no specific order is necessary, and the reviews may proceed simultaneously.

The Product License

Forms of somatic-cell and gene therapy that are successful in clinical trials will be produced commercially for use by qualified clinicians. Manufacturers of biologic products must hold licenses both for the products and for their manufacturing facilities. The FDA must therefore approve a sponsor's product-license application and establishment-license application for each product. Product-license applications contain detailed manufacturing information, product and labeling specifications, summaries of relevant preclinical data, and analyses of the design, conduct, and results of the clinical trials. The data are expected to demonstrate the ability to manufacture reproducibly a biologic product that provides overall benefit to patients when used in the clinic. The establishment-license application describes the manufacturer's facilities, including relevant procedures, equipment testing, and the qualifications of the personnel.

The pharmaceutical and biotechnology firms that are currently developing gene-therapy products will submit product-license applications and establishment-license applications for their products, as do producers of other biologic agents. The logistics of licensing cellular therapies will probably be more complicated because, like blood banking, cell processing may occur at local or regional facilities. For example, establishments that process and genetically modify patients' stem cells or other somatic cells might be located in or near tertiary care medical centers. Every such facility will need to be licensed by the FDA.

An Interactive Process

The FDA's Center for Biologics Evaluation and Research has worked with sponsors on hundreds of clinical research proposals for somatic-cell and gene therapy. Before IND applications are submitted, meetings between the center and sponsors planning clinical trials of new products are actively encouraged. Sponsors present the rationale for a particular approach, present preclinical data, discuss proposed trial designs, and otherwise describe their concepts and development plans. In the context of the specific product, the center's scientists describe standards for product characterization and quality control, comment on research strategies, pinpoint potential manufacturing problems, and suggest revisions in preclinical or clinical protocols.

To clarify some of the relevant issues, the Center for Biologics Evaluation and Research issued *Points to Consider in Human Somatic Cell Therapy and Gene Therapy* in 1991.[1] This document highlights many of the current scientific issues in the manufacture, testing, and clinical use of products for somatic-cell and gene therapy.

A Prudent Approach

Federal regulations provide that pharmaceutical research involving human subjects cannot begin until the FDA has determined that a clinical trial would not expose the subjects to an unreasonable and important risk of illness and injury, given the probability and magnitude of the risk and the potential benefits. This determination involves an assessment of both the product and the intended study population. For example, injecting genetically altered cells into a healthy person involves risk–benefit considerations different from those presented by studying an analogous therapy with possible antitumor properties in a patient with advanced cancer.

As the theoretical basis for somatic-cell and gene therapy has evolved, substantial concern has been voiced about its risks, both to individual patients and to the public at large, and its ethics. The public and the scientific community are well served, and the continuing development of new forms of technology is best ensured, by the independent, authoritative evaluation of risks that the FDA review process provides.

As these novel therapeutic applications are explored and knowledge about risks and benefits accumulates, the FDA's regulatory approach may well be modified. Nonetheless, early clarification of the agency's plan to apply its existing regulatory framework to products for somatic-cell and gene therapy is more prudent than waiting until the field has matured. This early discussion will facilitate product development by academic and commercial sponsors in line with FDA requirements and the demands of public health. The historical precedents for evaluating emerging forms of biologic technology are clearly established. Thoughtful and flexible science-based regulation under the statutory authorities that have evolved over the past century seems a consistent, reasonable, and prudent course.

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References

1 Food and Drug Administration. Points to consider in human somatic cell therapy and gene therapy. Rockville, Md.: Center for Biologics Evaluation and Research, 1991.

2 Public Health Service Act. 42 U.S.C. § 262, section 351.

3. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(g), section 201(g).
4. Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma: a preliminary report. N Engl J Med 1988;319:1676-80.
5. Riddell SR, Watanabe KS, Goodrich JM, Li DR, Agha ME, Greenberg PD. Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. Science 1992;257:238-41.
6. Epstein SL. Regulatory concerns in human gene therapy. Hum Gene Ther 1991;2:243-9.
7. Culver KW, Anderson WF, Blaese RM. Lymphocyte gene therapy. Hum Gene Ther 1991;2:107-9.
8. Culver KW, Berger M, Miller AD, Anderson WF, Blaese RM. Lymphocyte gene therapy for adenosine deaminase deficiency. Pediatr Res 1992;31:149A, abstract.
9. Rosenberg SA, Aebersold P, Cornetta K, et al. Gene transfer into humans — immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. N Engl J Med 1990;323:570-8.
10. Aebersold P, Kasid A, Rosenberg SA. Selection of gene-marked tumor infiltrating lymphocytes from post-treatment biopsies: a case study. Hum Gene Ther 1990;1:373-84.
11. Culver KW, Ram Z, Wallbridge S, Ishii H, Oldfield EH, Blaese RM. In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors. Science 1992;256:1550-2.
12. Anderson WF. Human gene therapy. Science 1992;256:808-13.
13. Pitman M. The regulation of biologic products, 1902-1972. In: Orecowald HR, Harden VA, eds. National Institute of Allergy and Infectious Disease: intramural contributions, 1887-1987. Washington, D.C.: Department of Health and Human Services, 1987:61-70.
14. Biologics Control Act of 1902. 32 Stat. 728

products intended for further manufacture when shipped from one legal entity to another and will be approved only when the final somatic cell therapy product is approved. For further discussion regarding shared manufacturing, refer to FDA's policy statement concerning cooperative manufacturing arrangements for licensed biological products, which was published in the Federal Register on November 25, 1992 (57 FR 55544).

In accordance with the statutory provisions governing biological products and drugs, a somatic cell therapy product or gene therapy product must be the subject of an IND in compliance with part 312 or of an approved PLA regardless of whether the finished product is shipped across State lines.

The manufacture of somatic cell therapy products or gene therapy products will involve many ancillary products used as part of the manufacturing process. The ancillary products are not intended to be present in final products but may have an impact on the safety, purity, or potency of the products under manufacture. Such ancillary products meet the definition of devices and, if marketed, will be regulated under the act device authorities, with the appropriate type of regulatory control being determined according to codified procedures (e.g., investigational device exemption (IDE)—21 CFR part 812; premarket approval (PMA)—21 CFR part 814, premarket notification (510(k))—21 CFR 870.81 through 807.97). When these ancillary products are used in the manufacturing of somatic cell or gene therapy products, they become subject to drug CGMP's, in particular for components and containers (21 CFR 211.80 through 211.94 and 211.101(b) and (c)).

Some of the ancillary products will already be marketed as medical devices, drugs, or biological products. When an ancillary product used as a component of the manufacturing process is marketed but not labeled for the specific use, such use may initially be described under the IND for the final somatic cell or gene therapy product. Such use of ancillary products by manufacturers of investigational somatic cell therapy or gene therapy products is contingent upon the submission of complete descriptions of the use of the ancillary product in the manufacturing process.

If the ancillary product used as a component of the manufacturing process does not have marketing approval, manufacturers of the somatic cell or gene therapy product must submit or provide cross-reference to a complete description of the manufacturing process, specifications qualification, and acceptance criteria of the ancillary product. This information may be filed by the sponsor of the IND for the somatic cell or gene therapy product, may be filed in an IND or IDE by the manufacturer of an ancillary product, or may be made available by the manufacturer of the ancillary product in a master file format, as defined in 21 CFR 814.3(d) and discussed in 21 CFR 814.20(c).

Manufacturers who wish to market ancillary products for use in the manufacturing of somatic cell or gene therapy products must file either: (1) A 510(k), (2) a PMA, (3) an amendment to an existing 510(k), PMA, NDA, or PLA.

The manufacture of somatic cell therapy products or gene therapy products may involve components of manufacture intentionally present as part of the final products. Products containing both a somatic cell component and another drug or device component in the final product will be handled as combination products.

The following statement succinctly describes FDA's current approach to regulating somatic cell therapy and gene therapy products with primary emphasis on premarket approval issues. As previously discussed, products that meet the biologic, drug, or device definition must also comply with other relevant provisions of the PHS Act and the act. Manufacturers may also find useful information in FDA's document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," Docket No. 91N-0428, available from CBER's Congressional and Consumer Affairs Branch (address above).

III. Statement

A. Somatic Cell Therapy

1. Definition

Somatic cell therapy is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics.

2. Cells Subject To Licensure as Final Products When Intended for Use as Somatic Cell Therapy

Cells subject to licensure as final biological products when intended for use as somatic cell therapy include cells manipulated to a way that changes the biological characteristics of the cell population (e.g., by expansion, selection, encapsulation, activation, or genetic modification as a part of gene therapy as defined in section III.B.1. of this document).

Examples include the following: (1) Autologous or allogeneic lymphocytes activated and expanded ex vivo (e.g., lymphokine-activated killer cells (LAK), tumor infiltrating lymphocytes (TIL cells), antigen specific clones), (2) encapsulated autologous, allogeneic, or xenogeneic cells or cultured cell lines intended to secrete a bioactive factor or factors (e.g., insulin, growth hormone, a neurotransmitter); (3) autologous or allogeneic somatic cells (e.g., hepatocytes, myocytes, fibroblasts, bone marrow- or blood-derived hematopoietic stem cells, lymphocytes) that have been genetically modified, (4) cultured cell lines; and (5) autologous or allogeneic bone marrow transplants using expanded or activated bone marrow cells. (For bone marrow products whose status is not clear, consult CBER.)

3. Cells and Tissues Subject to Licensure as Source Material

Cells and tissues subject to biological product licensure as source material include allogeneic or xenogeneic cells harvested by other than the final product license holder and intended for manufacture into a somatic cell product. Examples include the following: (1) Muscle cells removed from donors and shipped to a manufacturer for expansion into a muscle cell therapy, (2) animal cells harvested at an animal care facility and shipped to a manufacturer for encapsulation or other manufacturing steps into a somatic cell therapy, and (3) other human tissue harvested from donors and shipped to another legal entity for manufacture into a somatic cell therapy.

4. Cells for Which Applications for Approval Prior to Marketing are not Presently Required

Cells for which applications for approval prior to marketing are not required at the present time include the following: (1) Cell transplants not having the characteristics described in sections III.A.2. and III.A.3. of this document, and (2) minimally manipulated or purged bone marrow transplants. Examples include the following: (1) Allogeneic bone marrow transplantation employing ex vivo T cell purging with a monoclonal antibody approved for such purging, (2) autologous bone marrow transplantation employing ex vivo tumor cell purging by an approved agent, and (3)

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United States House of Representatives
Committee on Science, Space and Technology
Representative George Brown, Chairman

Hearing On Gene Therapy- Status, Prospects for the Future and Government Policy Implications
Sept. 28, 1994

Written Comments of
Abbey S. Meyers
President
National Organization for Rare Disorders (NORD)

Mr. Chairman, members of the Committee, we are pleased that you are reviewing the status of gene therapy research in the United States, and we wish to provide some thoughts from the perspective of rare "orphan disease" patients and families who have invested a great deal of hope in the success of this new technology

I am Abbey S Meyers, President of the National Organization for Rare Disorders (NORD), and a member of the NIH Recombinant DNA Advisory Committee (RAC). Of the broad spectrum of divergent interests participating on the RAC, I represent the consumer community. However, for the purpose of this hearing I am submitting this testimony <u>not</u> as a member of the RAC, but as President of NORD, a non-profit voluntary health agency representing the interests of an estimated 20 million Americans with rare disorders Under the Orphan Drug Act of 1983, a "rare disorder" is defined as an illness or condition effecting fewer than 200,000 Americans. There are approximately 5,000 of these ailments, and about 4,000 of them are genetic.

What has been accomplished with the use of gene therapy? Where is gene therapy and related research headed?

Mr. Chairman, when gene therapy was first conceived, it was visualized as a technology that might correct genetic defects and treat or prevent hereditary disorders However, despite highly publicized news stories to the contrary, human gene therapy has veered far off course Today approximately 80% of RAC approved gene therapy protocols are <u>not for genetic diseases</u>, but instead for cancer They are <u>not attempts at correcting genetic defects</u>, but rather are experiments aimed at using viruses as drug delivery systems. Most current gene therapy experiments are <u>not innovative scientific exercises</u> with a therapeutic intent, but rather they are "me-too" experiments that copy protocols previously underway In fact most gene therapy protocols are not "therapy", they are simply "gene transfer" experiments aimed at learning whether vectors can transfer genes to human cells.

Human gene therapy does offer the promise of cures, prevention and treatments that mankind has been waiting for. But scientific excellence is not driving the issue, Wall Street is Vector manufacturers see little potential profit in developing gene therapy for most hereditary diseases, whereas they envision extensive profits from cancer. Therefore, biotechnology companies are generally sponsoring protocols that differ only minutely from each other, aimed at delivering interleukin, interferon and other biologic substances directly into tumor cells, even though we already know from experiments underway that if the transferred gene has any effect at all, it has a short lived temporary effect that lasts no more than a few days.

On the other hand, the few gene therapy trials that have shown a therapeutic effect involve genetic diseases. Ashanti DeSilva and other children with Severe Combined Immune Deficiency (SCID) have illustrated how the replacement of defective genes in hereditary diseases could possibly halt or reverse the disease process. However, there is controversy about the actual effect of gene therapy on the 5 children with SCID who are also using an enzyme replacement drug called Adagen (PEG-ADA). It has not been conclusively shown that the clinical improvement in the children is from the drug or the genes, or perhaps both

Dr. James Wilson's experiment replacing the genes for cholesterol receptors in the livers of people with Familial Hypercholesterolemia have opened the window of opportunity to treat dozens of painful and crippling disorders characterized by liver enzyme deficiencies. However, there are no other protocols underway for these other diseases, most likely because there is no incentive for commercial vector manufacturers to investigate liver diseases with limited populations. Yet everyone agrees these are the very diseases that might benefit most from gene therapy.

Naturally, companies entering the field of gene therapy must attract financing, usually from venture capitalists. As long as this emerging technology is driven by Wall Street, not scientific opportunity, the corporate mentality will continue to drive the direction of gene therapy research off course When companies do support gene therapy experiments on hereditary diseases they will continue to focus on a limited number of disorders where they see the most potential for profit For example, there are to date approximately 3 approved experiments on Gaucher's disease, which is estimated to effect about 5,000 symptomatic patients in the United States. About 1,000 of these patients are currently paying $150,000 to $300,000 per year for a biotechnology drug (which is the only available treatment), so vector manufacturers are convinced that the market is lucrative for this disease. There are also approximately seven protocols for cystic fibrosis which effects about 30,000 Americans CF is also a very expensive disease to treat, due to repeated hospitalizations, required medical equipment and expensive drugs No other lung diseases are the subject of gene therapy protocols.

In the context of government policy options, we believe that the government should take a strong hand in directing the future of gene therapy strategies for hereditary diseases, because in the absence of government direction genetic disease research will not be adequately pursued by the private sector. Venture capitalists want quick payoffs, but science cannot be speeded to satisfy investors The cover story of the September 26th issue of Business Week superbly describes this problem: "Gene therapy's financial doldrums . . . reflect the vast gulf between promise and product".

What are the ethical issues?

There are many ethical issues that must be addressed when considering that science is trying to develop techniques that can change the genetic makeup of human beings, and potentially the human race.

Human gene therapy must be regulated, for if it is not, there is a real danger that some scientists might try to change genes for the sake of human enhancement and not for the correction of diseases, or that future generations might be effected causing freakish birth defects. The temptation can be great to make a person a little taller, a little thinner, a little more intelligent, but once this is permitted, there is no predicting where it will stop. The consequences of such action could potentially change humanity forever. Diversity is the essence of humanity, and it would be a great mistake to allow any scientist power to change future generations, especially since our offspring cannot give permission in advance.

On the other side of the issue is the deep rooted fear of the public that science fiction novels might come to life if someone does not prevent Frankenstein type experiments, or if contaminating virus's are released into the environment This is the reason that the RAC is required to hold public meetings, and the public is permitted to have input on gene therapy experiments. When gene therapy experiments started, the Foundation for Economic Trends sued NIH to assure that RAC meetings remained public. The openness with which these meetings are conducted serves to assure our citizens that moral and ethical issues are weighed with equal attention to scientific issues

Recently, an NIH experiment using the drug FIAU as a treatment for hepatitis killed several patients. Families of those patients are suing NIH on the grounds that the informed consent documents, which the patients signed, were untruthful and inadequate The informed consent document is a very important component of clinical research, and especially for a new technology with unknown long-term effects. The RAC is the forum where public discussion of informed consent documents has reinforced the concept of patient's rights, significantly reducing the public's fear that "mad scientists" might reengineer the human race behind closed doors. It is obvious that many participants in gene therapy development have their own interests at heart (e.g., academic institutions, scientists, vector manufacturers, etc.), but the RAC is the independent body that has no vested interest and no ax to grind. It is there solely to protect the public.

Moreover, the openness of RAC deliberations enhances communications within and among the scientific community If gene therapy is left to the private sector, most information would be proprietary and scientists would be unable to learn from each other's successes as well as failures. Recently, a serious adverse event in one patient was quickly communicated to other clinicians conducting similar experiments, thereby preventing serious consequences and perhaps even death in other patients If this clinical trial were protected as a commercial secret, such communication would not have been possible

What is the importance of gene therapy on international competitiveness, jobs and markets for U.S companies?

The United States is the acknowledged leader in gene therapy No other country is close to our scientists in the understanding of genetic transfer Indeed, at every RAC meeting representatives of foreign countries attend and thank us for keeping our deliberations public so they can learn not only about scientific issues, but ethical issues that their nations have only begun to address This has led to demands for the British government to open their scientific meetings to the public (Nature, Vol 371, September 15, 1994).

However, the scientific leadership of the United States will not remain unchallenged if we continue to see so many "me-too" repetitive experiments on the same diseases. We are not developing enough new vectors, and sometimes it seems that American scientists are simply avoiding challenge by doing "easy" experiments. Perhaps it is easier to obtain funding for something that has already been done, but the fact is we have not seen any breakthroughs on cancer using current protocols Fresh new ideas are needed, and scientists who are willing to undertake risky ideas, especially on diseases they think they can cure even though there might not be a large and lucrative market. The private sector is simply not equipped to pioneer new gene therapy techniques when it relies so heavily on venture capital, so obviously the NIH should expand its role in support of pioneering experiments.

We ought to find ways that this industry can survive without relying so heavily on Wall Street. When the Japanese target an industry for world leadership, the government subsidizes long term development In our country investors want a short term pay-off but, unfortunately, gene therapy will need many more years before commercialization is possible.

What are the issues concerning regulation as gene therapy products come closer to commercialization?

First, it is important to remember that gene therapy is not at all close to commercialization. All approved protocols are for phase 1 studies. There are no phase II studies, and no proof of efficacy has been established. There are indications in the SCID and hypercholesterolemia studies that they may be effective on some humans, but no one has been cured and too few humans have been tested.

Scientific progress, not the RAC, is holding up the commercialization of gene therapy. The fact is **we still don't know if it will work** to prevent or ameliorate disease.

It is much too premature to think about streamlining the approval process for the sake of commercialization Indeed, the FDA must be doubly vigilant to assure that disasters do not occur in the initial gene therapy patients because serious adverse events, or contamination of the vectors or of the environment, might jeopardize the future of all gene therapy experiments. For this reason we are comforted by the fact that FDA is monitoring the field closely and developing standards that companies must comply with. It is unfortunate that FDA's standards might drive up the cost of vector manufacturing, which may make it even more difficult for academic scientists with no commercial sponsor to conduct clinical trials. However, FDA's RCR testing standards were established with public discussion at the RAC, and they are absolutely essential to assure safety

We would like to see the federal government develop a vector manufacturing and testing facility that could be used by academic investigators who wish to develop new treatments for unstudied diseases. If only one or two of these facilities could be approved by FDA, there might be an economy of scale that would make the technology more affordable to academic scientists. Similarly, NIH should create a research grant program for gene therapy for hereditary diseases so that this field does not remain dominated by cancer research. Moreover, the RAC is currently able to make its judgments based solely on safety issues, and it has admittedly approved experiments that are not "good science". RAC should be able to deny approval for protocols that are irrelevant to advancement of knowledge and have no chance of success.

The RAC review procedure cannot and should not be dismantled RAC, FDA and ORDA are absolutely committed to enhancing the development of this field. Since many gene therapy experiments are duplicative of current protocols, the RAC will not review them but information about them must remain available to the public. We should not, at this very early stage, permit the gene therapy research process to be clouded in veils of secrecy. **If the public has raised concerns about simple matters such as genetically engineered tomatoes, and growth hormone in milk, the government must assure the public that truth is not being hidden and nazi-like medical experiments are not being conducted in secret.** The public cares about this process Mr. Chairman, and continuing government oversight of the gene therapy field is paramount to maintaining the public's trust, and assuring the safety of patients

The government should do everything it can to encourage collaboration between academia and biotechnology companies while maintaining the environment of openness and public trust Something seems to happen when an area of science becomes commercialized and information is deemed proprietary. Collaboration stops, public trust diminishes, and young scientists turn elsewhere where the shroud of secrecy does not inhibit their freedom to publish America should continue to lead the world in gene therapy research, but we should never allow the tail to wag the dog. This is exactly what will happen if oversight and regulation are reduced.

There is no constituency in this nation that wants to see advancements in gene therapy more than the family of genetic disease patients, and Mr. Chairman I do not have to remind you that all of us have some genetic defect. Keeping the process open, and having frank discussions about scientific and ethical issues is essential for the advancement of science Despite the headline claims in the tabloids about the miracles of gene therapy, there have not yet been documented miracles. A lot of false hopes have been raised. We know in our hearts that there will indeed be miracles someday if we can redirect this area of science that has veered off course Gene therapy, as it was originally envisioned, should correct, treat and cure genetic diseases. It is our hope that the government can help to put this engine of the future back on course.

The field of gene therapy is just the tip of the iceberg. Its success to date reflects the return on investment our government has made for many years in basic science including recombinant technology, monoclonal antibodies, transplantation, basic virology, the human genome project and other related biomedical research. The RAC is not a body of government beurocrats, but rather members of the public, scientists, attorneys, ethicists and patients A technology with potential for profound impact on all of humanity, both current and future generations, must continue to undergo public scrutiny As a society we owe this to our offspring, we owe this to the taxpayer, and we owe this to science

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